

# Prognostic implications of myocardial injury around percutaneous coronary interventions

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# Prognostic Implications of Myocardial Injury around Percutaneous Coronary Interventions

**Marcus Bernardus Nienhuis**

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# Prognostic Implications of Myocardial Injury around Percutaneous Coronary Interventions

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# Chapter 1

# General introduction and outline of the thesis

In the last decades of the twentieth century, treatment of patients with coronary artery disease has changed dramatically. After the introduction in 1977 by Andreas Gruentzig [1], the importance of percutaneous coronary interventions (PCI) in the treatment of patients with coronary artery disease is still rising, with beneficial effects on both morbidity and mortality. Balloon angioplasty was the principal mode of performing PCI in the first years. Nowadays (drug-eluting) stent implantation is mostly performed. Stent implantation is effective in the management of (iatrogenic) coronary dissection during PCI and reduces restenosis [2-4]. Other techniques of PCI such as cutting balloon or atherectomy devices are only indicated in specific cases [5,6].

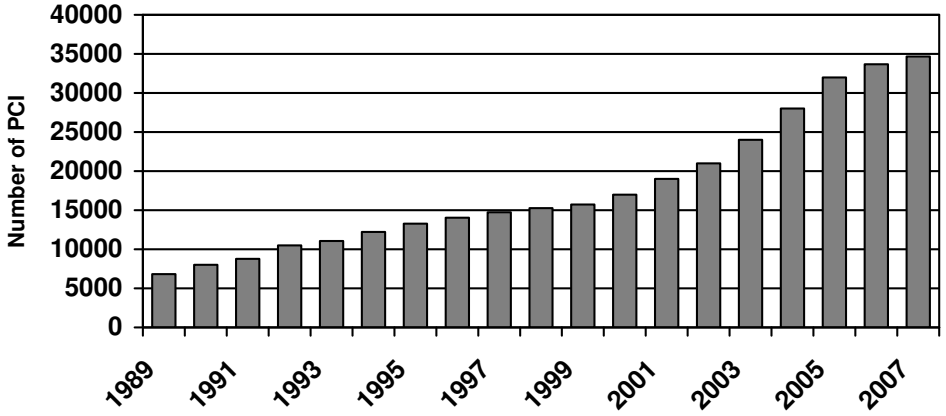


**Figure 1.** Number of PCI in the Netherlands throughout the years (7).

As in many other countries, in the Netherlands the number of PCIs has increased rapidly (figure 1) [7]. In 2007, nearly 35,000 PCIs were performed, whereas a number of more than 40,000 interventions has been postulated for 2010 [8]. Only a part of this rise can be explained by the use of PCI instead of coronary artery bypass grafting (CABG). Another important explanation is the more invasive approach of patients with acute coronary syndromes (ACS), especially ST-elevation myocardial infarction (STEMI).

As the number of PCIs is growing, quality control and the monitoring of efficacy as well as safety is of growing importance. Markers of complications of PCI can be helpful to identify patients needing more aggressive or different additional therapy. Furthermore, these markers can be helpful in improving PCI success, by validating new techniques and medications around PCI directly, instead of

awaiting long-term clinical effects for every new therapy. One manner of monitoring complications of PCI is by measuring cardiac biomarker elevations after PCI.

**Myocardial injury**

Cardiac enzymes have been shown to be strongly related with myocardial injury, infarct size and prognosis in patients with acute myocardial infarction (MI) [9,10]. Especially tests for creatine kinase (CK) and tests for the muscle-brain dimer CK-MB are used throughout the world to diagnose MI for many years [11,12]. However, cardiac troponins have been shown to be superior in establishing diagnosis and prognosis in patients with suspected ACS [13-15]. Therefore, nowadays, the troponins are the preferred biomarkers to diagnose MI, according to the most recent definition of MI [16]. The time course of elevations of the different serum biomarkers after MI are shown in figure 2 (adapted from Braunwald [17]).

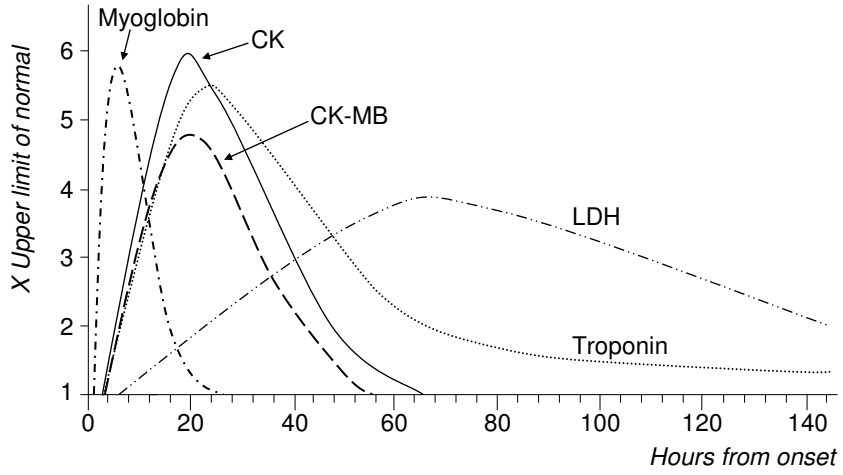


**Figure 2.** Time course of serum markers in myocardial infarction

***PCI for stable angina***

Elevations of cardiac enzymes can be observed frequently after (elective) PCI, with reported rates between 6 and 48%, and have been associated with cardiac events during follow-up. This has been demonstrated in particular for elevations of CK and CK-MB [18-21]. As the diagnostic value of troponin is superior compared to CK(-MB) in patients with (suspected) ACS, the prognostic value of troponin elevation after PCI, compared to CK(-MB), may be superior as well. However, conflicting results are reported about the association between troponin elevation and cardiac events and/or mortality during follow-up [21-23].

***PCI for ST-elevation myocardial infarction***

The association between cardiac enzymes, infarct size and mortality during follow-up was demonstrated in patients undergoing no reperfusion therapy or thrombolysis for STEMI. However, primary PCI has become the preferred therapy of patients with STEMI, provided the procedure is performed in a timely manner by experienced operators [5,6,24,25]. As reperfused hearts might release cardiac enzymes in the systemic circulation in different levels and time courses, the predictive values of the enzymes might differ in these patients compared to those undergoing no or less effective reperfusion therapy [26].

***PCI for other acute coronary syndromes***

The number of PCI performed in patients with non-STEMI and/or unstable angina forms a substantial part of the total number of PCI, and it is expected to be the most frequent indication for PCI in the near future in the Netherlands [8]. Patients with non-ST-elevation ACS have an adverse prognosis, even when treated with early PCI, possibly because of both delayed time-to-hospital arrival and increased door-to-balloon time [27,28]. Although a lot of studies on patients undergoing PCI for non-ST-elevation ACS have been published [29-32], only few studies report on enzyme release after PCI in these patients. Moreover, these studies have enrolled heterogenous patient populations [21,33].

**This thesis**

The main objective of the studies presented in this thesis is to investigate the clinical value of cardiac biomarkers after PCI, especially troponin T (TnT), CK and CK-MB. The importance of these biomarkers is evaluated in patients undergoing elective PCI as well as in patients undergoing primary PCI for STEMI.

**Part I** of this thesis is focused on myocardial injury after elective PCI.
The **second chapter** describes the results of a prospective study on 713 unselected patients undergoing elective PCI, investigating the prognostic importance of postprocedural elevation of either TnT or CK.
The influence of pre-treatment with clopidogrel on myocardial necrosis after elective PCI, defined by small postprocedural TnT elevation, is assessed in the prospective observational study including 656 patients described in the **third chapter**.
In the **fourth chapter**, differences in TnT elevation between multivessel and single-vessel PCI are studied in the same cohort as described in chapter 2. Furthermore, differences in cardiac events during follow-up are investigated, according to the type of index-PCI.
The **fifth chapter** is a review of the currently available data with regard to the prognostic value of troponin elevation after elective PCI. The association between postprocedural troponin elevation and mortality and/or myocardial infarction during follow-up is investigated in this meta-analysis, involving 15,581 patients.

**Part II** of this thesis is focused on myocardial injury around primary PCI.
In the **sixth chapter**, the value of TnT on admission in patients with STEMI is investigated. The predictors of elevated TnT on admission and its prognostic value are evaluated in this study in 444 patients undergoing primary PCI.
In chapter 7 and 8, the findings of 14 years of primary PCI experience in Zwolle are presented. All 4,990 patients are studied in chapter 8, whereas patients who died within 2 days after PCI were excluded in chapter 7.
The prognostic values of CK and CK-MB are investigated in 4,670 patients undergoing primary PCI for STEMI in the **seventh chapter**. The association between peak-CK and peak-CK-MB levels, left ventricular function and one-year follow-up is assessed.
The predictive values of long-term mortality of infarct location, enzymatic infarct size and LV ejection fraction are compared in the **eighth chapter**. Whether infarct location is an independent predictor of prognosis, even after correction for enzymatic infarct size, is also evaluated in that study.

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# Part I

# Myocardial injury after elective PCI

# Chapter 2

# Prognostic importance of troponin T and creatine kinase after elective angioplasty

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**ABSTRACT**

**Background:** The prognostic importance of elevated cardiac enzymes after elective percutaneous coronary intervention has been debated. Therefore, we performed a prospective observational study to evaluate the prognostic value of postprocedural rise of troponin T and creatine kinase.

**Methods:** Troponin T (cut-off value 0.05 ng/ml) and creatine kinase (cut-off value 180 IU/l with muscle-brain fraction >4%) were measured 12 hours after elective percutaneous coronary intervention in 713 consecutive patients without elevated troponin before the procedure. Primary endpoint was the combined incidence of death, myocardial infarction, stroke, repeat angiography or re-admission because of anginal symptoms during the follow-up period.

**Results:** Troponin was elevated after the procedure in 150 patients (21%) and creatine kinase in 66 pts (9%), with a strong association between increased troponin and creatine kinase. After a mean follow-up of 10.9 months, mortality was low (1%) and not associated with increased troponin or creatine kinase. There was, however, a strong relation between postprocedural troponin and re-admission for angina (p=0.001) or myocardial infarction (p=0.001). Furthermore, troponin rise was significantly associated with an increased risk of the primary endpoint (relative risk 1.55 95% confidence interval 1.01-2.38). After multivariate analysis, troponin elevation but not increased creatine kinase was associated with an increased risk of the primary endpoint (relative risk 1.59 95% confidence interval 1.02 - 2.47 for troponin elevation versus 1.16 95% confidence interval 0.62-2.15 for increased creatine kinase).

**Conclusion:** Increase of troponin T after elective percutaneous coronary intervention has stronger prognostic implication when compared to increased creatine kinase.

## Introduction

Cardiac-specific troponins are useful in establishing diagnosis and predicting prognosis in patients with suspected acute coronary syndromes. In these patients, troponin has higher sensitivity and specificity compared to creatine kinase or its MB isoform (CK-MB) [1-4].
After elective percutaneous coronary intervention elevated cardiac enzymes can be observed even if the procedure is angiographically successful and uncomplicated. Elevations of CK-MB have been associated with an increased risk of repeat revascularisation, acute myocardial infarction and death (major adverse cardiac events, MACE) [5-8]. Despite the high sensitivity and specificity of troponin in acute coronary syndromes, there are conflicting results about the prognostic significance of increased troponin after elective percutaneous coronary intervention [9-24]. However, most studies report only a small number of patients [9-11,17-24]. Moreover, some studies include also patients with an acute coronary syndrome, which could have influenced the results [8,16,21].
To assess the incidence and predictive value of creatine kinase or troponin T elevation after elective percutaneous coronary intervention in daily practice, the current prospective study was designed.

## Methods

*Study population*
It concerns a prospective, observational study [25]. The patient cohort included unselected patients who underwent elective percutaneous coronary intervention between June 2002 and August 2003 in the Isala klinieken, Zwolle, the Netherlands. All patients had symptomatic coronary artery disease with objective evidence of ischemia. Patients with percutaneous coronary intervention for ST elevation myocardial infarction were excluded, as well as patients with urgent percutaneous coronary intervention for acute coronary syndromes.

*Procedure and laboratory testing*
All angiographic and percutaneous coronary intervention procedures were performed according to the standard protocol. Routine care before and after the procedure was undertaken for all patients, including preprocedural use of aspirin and a bolus of intravenous heparin (5000 U) at the beginning of the procedure. All

patients received a loading dose of 300 mg clopidogrel before the procedure, followed by 75 mg once daily for at least 28 days after the percutaneous coronary intervention. Use of glycoprotein IIb/IIIa receptor inhibitors or stents was left to the discretion of the interventional cardiologist. At the time the study was performed, the use of drug eluting stents was less than 10%.

A blood sample was routinely obtained from all patients just before the interventional procedure in the catheterisation room. The second sample was taken 08.00 a.m. the day after, at least 12 and at maximum 22 hours after the procedure. All samples were prepared and stored locally in our core laboratory at -70°C until analysed. Troponin T was analysed using the third generation troponin T test (Roche diagnostics, Mannheim, Germany) with a threshold of 0.01 ng/ml. Although the 99th percentile of normal troponin T may be as low as 0.01 ng/ml, according to other recent studies we used 0.05 ng/ml as cut-off value [26-29]. Separate analyses were performed using 0.03 ng/ml as cut-off value. However, as we pre-specified a cut-off value of 0.05 ng/ml, the final analyses were performed with this cut-off value for troponin T. Rise of creatine kinase level above 180 IU/L together with CK-MB > 4% was defined as elevated creatine kinase [30].

*Clinical follow-up*

Clinical outcomes were obtained at least 30 days after percutaneous coronary intervention by telephone interviews with the patient, their relatives or their cardiologist or primary physician. Using a standardised format, information about repeat coronary angiography, repeat revascularisation, myocardial infarction, cerebrovascular accident, re-admission because of angina and death was collected. All details about clinical events were also obtained from the medical files.

Myocardial infarction during follow-up was defined as new onset of Q waves or creatine kinase and CK-MB elevation above cut-off values. All deaths during follow-up were considered of cardiac cause.

*Statistical analysis*

All analyses were performed with SPSS statistical software (SPSS Inc., Chicago, Illinois). Group comparisons were done by the chi-square test for proportions and Student t test for continuous variables. Primary endpoint was defined as the combined incidence of death, myocardial infarction, stroke, repeat angiography or re-admission because of anginal symptoms during the follow-up period.

To assess the potential association between increasing enzymes and increasing incidence of the primary endpoint, patients were categorised in three groups. Patients without increased enzymes consisted of the control group. Patients with increased enzymes were divided into two groups, using the median value of the whole group of patients with increased enzymes as the cut-off value between the second and third group, thereby creating an equal number of patients in the latter 2 groups (TnT 0.13 ng/ml, CK 250 IU/L).
Multivariate analyses (logistic regression analyses) were performed to assess the independent association between increased troponin T or creatine kinase after the procedure and the occurrence of cardiac events in follow-up. A value of $p < 0.05$ was considered significant.

**Results**

During enrolment, 745 patients were screened for our study. Of these 745 patients, a total of 713 patients (96%) had no elevated troponin T (<0.05 ng/ml) before the percutaneous coronary intervention, representing the final study group. Mean age was 64 years (SD 10.3), 211 patients (30%) were female and 127 patients (18%) had diabetes. Multivessel disease was present in 344 patients (48%) and 111 patients (16 %) had angina with CCS class 4. A total of 501 patients (70%) were treated with a stent and 146 patients (20%) had angioplasty of more than 1 vessel. Percutaneous coronary intervention of a bypass graft was performed in 25 patients (4%). 54 patients (8%) received glycoprotein IIb/IIIa receptor inhibitors. Increased troponin T (>0.05 ng/ml) after the procedure was documented in 150 patients (21%) (mean in this group 0.29 ng/ml, SD 0.51; range 0.051-3.98) and increased creatine kinase in 66 patients (9%) (mean creatine kinase in this group 325 IU/L, SD 217; range 180-1187). Furthermore, 684 patients (96%) had preprocedural and 463 patients (65%) had postprocedural undetectable levels of troponin T (<0.01 ng/ml).
Baseline variables according to elevated troponin T (>0.05 ng/ml) after the percutaneous coronary intervention are shown in table 1. Patients with troponin T elevation more often had creatine kinase elevations (32%) compared to those without increased troponin T (3%, $p <0.001$).

**Table 1.** Baseline characteristics of 713 pts after elective PCI without increased troponin (<0.05 ng/ml) before the PCI according to increased troponin (>0.05 ng/ml) after the PCI.

| | Troponin not increased (n=563) | Troponin increased (n=150) | P |
|---|---|---|---|
| Age, yrs | 63.5 (±10) | 63.7 (±11) | 0.84 |
| Female | 172 (31) | 39 (26) | 0.28 |
| Risk factors | | | |
| Diabetes mellitus | 108 (19) | 19 (13) | 0.06 |
| Hypercholesterolemia | 316 (69) | 82 (68) | 0.94 |
| Smoking | 179 (33) | 51 (35) | 0.61 |
| Hypertension | 249 (49) | 62 (48) | 0.80 |
| Family history of coronary artery disease | 195 (37) | 55 (40) | 0.59 |
| Multivessel disease | 265 (47) | 79 (53) | 0.22 |
| Medical history | | | |
| Myocardial infarction | 249 (44) | 70 (47) | 0.56 |
| Percutaneous coronary intervention | 148 (26) | 41 (27) | 0.81 |
| Coronary bypass grafting | 68 (12) | 16 (11) | 0.63 |
| Cerebrovascular accident | 38 (6.7) | 13 (8.7) | 0.42 |
| Percutaneous coronary intervention | | | |
| RCA | 165 (29) | 35 (23) | 0.15 |
| LAD | 239 (43) | 60 (40) | 0.59 |
| Multivessel PCI | 100 (18) | 46 (31) | 0.001 |
| Stent | 395 (70) | 106 (72) | 0.73 |
| CCS4 | 81 (14) | 30 (20) | 0.09 |

Mean or number (sd or %)

Table 2 shows baseline variables according to increased creatine kinase after the percutaneous coronary intervention. After multivessel percutaneous coronary intervention there was a significant increase of both troponin T and creatine kinase. Only 11 patients (1.5 %) had after the PCI suboptimal blood flow, defined as Thrombolysis In Myocardial Infarction (TIMI) flow less than 3. Of these patients, 3 had elevated troponin T and CK after the procedure (NS). Accordingly, observed TIMI flow after the PCI could not explain the majority of increased TnT or CK.

Mean follow-up was 10.9 months (SD 10.6), and 30-day follow-up was available in all patients. The primary endpoint was documented in 139 patients (19.5%) and was significantly observed more often in patients with diabetes, multivessel disease or multivessel percutaneous coronary intervention. Also patients with a previous revascularisation by either percutaneous coronary intervention or coronary artery bypass grafting had a higher incidence of the primary endpoint.
Differences between patients with and without elevated cardiac enzymes with regard to events during the follow-up period are shown in table 3.

**Table 2.** Baseline characteristics of 713 pts after elective PCI without increased troponin (<0.05 ng/ml) before the PCI according to increased creatine kinase (>180 IU/L with CK-MB >4%) after the PCI.

| | Creatine kinase not increased (n=647) | Creatine kinase increased (n=66) | P |
|---|---|---|---|
| Age, yrs (sd) | 63.3 (±10.4) | 65.3 (±10.0) | 0.15 |
| Female | 193 (29.8) | 18 (27.3) | 0.67 |
| Risk factors | | | |
| Diabetes mellitus | 114 (17.6) | 13 (20.0) | 0.63 |
| Hypercholesterolemia | 357 (67.7) | 41 (77.4) | 0.15 |
| Smoking | 213 (33.8) | 17 (27.0) | 0.28 |
| Hypertension | 283 (49.2) | 28 (47.5) | 0.80 |
| Family history of coronary artery disease | 219 (36.6) | 31 (50.8) | 0.03 |
| Multivessel disease | 264 (44.3) | 26 (41.3) | 0.97 |
| Medical history | | | |
| Myocardial infarction | 295 (45.7) | 24 (36.9) | 0.18 |
| Percutaneous coronary intervention | 170 (26.3) | 19 (28.8) | 0.67 |
| Coronary bypass grafting | 77 (11.9) | 7 (10.6) | 0.76 |
| Cerebrovascular accident | 45 (7.0) | 6 (9.1) | 0.52 |
| Percutaneous coronary intervention | | | |
| RCA | 183 (28.3) | 17 (25.8) | 0.66 |
| LAD | 272 (42.0) | 27 (40.9) | 0.86 |
| Multivessel PCI | 126 (19.5) | 20 (30.3) | 0.04 |
| Stent | 453 (70.1) | 48 (73.8) | 0.53 |
| CCS4 | 105 (16.2) | 6 (9.1) | 0.13 |

Mean or number (sd or %)

**Table 3.** Events during follow-up of 713 pts after elective PCI without increased troponin (<0.05 ng/ml) before the PCI according to increased troponin (>0.05 ng/ml) and increased creatine kinase (>180 IU/L) after the PCI.

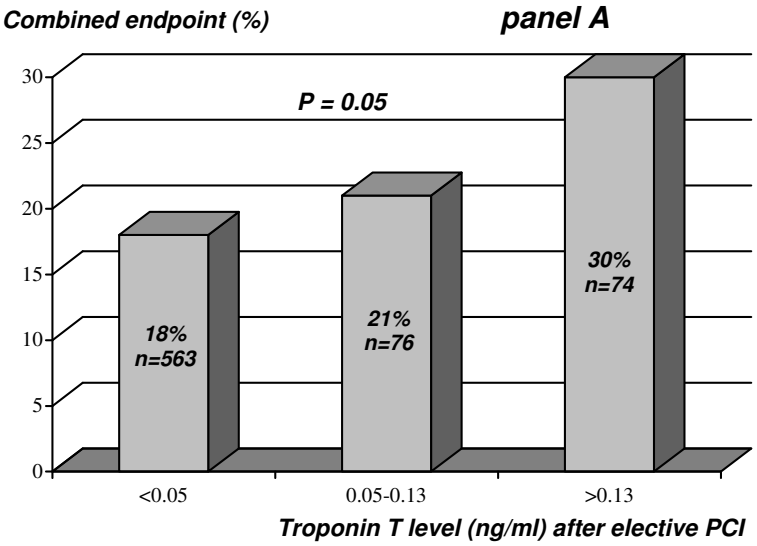
| | Troponin not increased (n=563) | Troponin increased (n=150) | P | Cr.kinase not increased (n=647) | Cr.kinase increased (n=66) | P |
|---|---|---|---|---|---|---|
| Death | 9 (1.6) | 0 | 0.12 | 9 (1.4) | 0 | 0.34 |
| Myocardial infarction | 3 (0.5) | 6 (4.1) | 0.001 | 4 (0.6) | 5 (7.8) | 0.001 |
| Coron. angiography | 55 (9.8) | 21 (14) | 0.14 | 67 (10.4) | 9 (13.6) | 0.41 |
| Re-PCI | 42 (7.5) | 16 (10.7) | 0.20 | 51 (7.9) | 7 (10.6) | 0.44 |
| CABG | 12 (2.1) | 3 (2.0) | 0.92 | 15 (2.3) | 0 | 0.21 |
| Stroke | 7 (1.2) | 2 (1.3) | 0.93 | 7 (1.1) | 2 (3.0) | 0.18 |
| Re-admission | 50 (9.0) | 29 (19) | 0.001 | 67 (10.5) | 12 (18.2) | 0.06 |
| Combined endpoint | 101 (17.9) | 38 (25.3) | 0.04 | 124 (19.2) | 15 (22.7) | 0.49 |

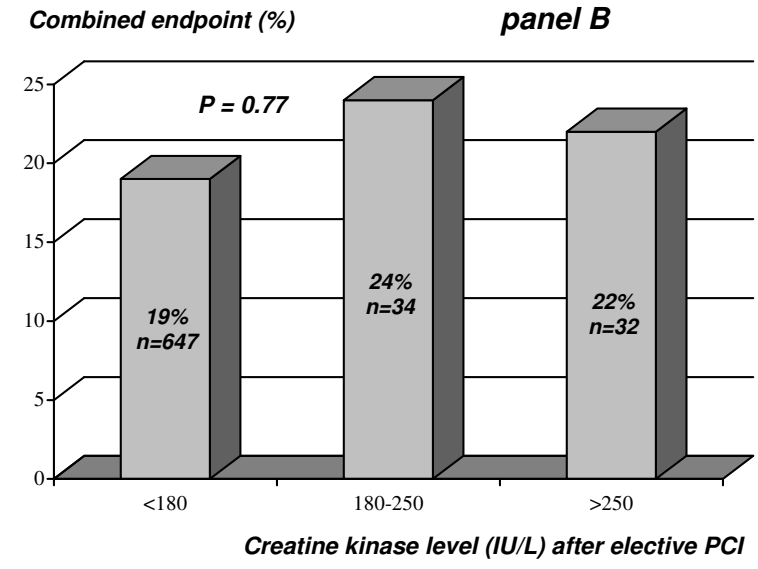
Number (%)

Mortality was low and neither associated with elevated troponin T nor creatine kinase. There was, however, a strong association between the occurrence of myocardial infarction and postprocedural increase of both troponin T and creatine kinase. Increased troponin T was also associated with re-admission for anginal complaints. Increased troponin T but not increased creatine kinase was associated with increased incidence of the primary endpoint. There was also an association between increasing troponin T after the percutaneous coronary intervention and increasing incidence of the primary endpoint (figure 1, panel A). There was no association between categories of increased creatine kinase and the primary endpoint (figure 1, panel B).

To assess the independent association between increased troponin T or creatine kinase and the primary endpoint, multivariable analyses were performed. The unadjusted odds ratio of increased creatine kinase was 1.24 (95% CI 0.68-2.28). After adjusting for differences in age, gender, multivessel percutaneous coronary intervention, diabetes and angina class, the odds ratio of increased creatine kinase for the incidence of the primary endpoint was 1.16 (95% CI 0.62-2.15). The unadjusted odds ratio of increased troponin T was 1.55 (95% CI 1.01-2.38). After multivariable analyses, the odds ratio of increased troponin T for the incidence of the primary endpoint was 1.59 (95% CI 1.02-2.47).
Using 0.03 ng/ml as cut-off value for troponin T elevation, patients with increased troponin T after the procedure had the combined endpoint in 26.6% compared to 17.0% of patients without increased troponin T ($p = 0.004$).

**Figure 1.** Association between categories of troponin T (panel A) or creatine kinase (panel B) and the incidence of the combined clinical endpoint after elective percutaneous coronary intervention in 713 patients.



## Discussion

The present study shows an association between troponin T rise after elective percutaneous coronary intervention and cardiac events during follow-up. Mortality in this low-risk population was low, and was neither associated with troponin T nor creatine kinase increase. Increased creatine kinase was only significantly associated with myocardial infarction during follow-up. In patients with elective percutaneous coronary intervention, the prognostic value of troponin T is more important than creatine kinase.

*Mechanism*

There may be several explanations for the worse prognosis of patients with enzyme increase after elective percutaneous coronary intervention. It has been demonstrated that troponin increase after percutaneous coronary intervention was associated with more complex procedures, with prolonged inflation times, complex lesion morphology [17] and more often side branch occlusion [31]. Also, patients with troponin elevation may have an increased systemic inflammatory state [32]. Magnetic resonance imaging studies showed that even small increases of cardiac markers (either CK-MB or Troponin I) after percutaneous coronary intervention are associated with new irreversible myocardial injury [33,34]. The adverse consequences of myocardial damage caused by percutaneous interventions may be similar to spontaneous myocardial damage [7]. Another explanation for the worse prognosis is that troponin increase is caused by microembolism [35].

*Previous literature*

In comparison with other studies with a similar follow-up period, the event rate in our study was low. The average long-term incidence of the combined endpoint of death, myocardial infarction or recurrent revascularisation in four other comparable studies was 19.1%, compared to 12.8% in our study [10,12,20,23]. Mortality in our patient cohort was 1.3 % compared to 3.8% in the four previous studies. Cavallini et al, recently showed a linear association between 2-years mortality and CK-MB elevation, but did not find such relation between troponin I elevation and death [8]. However, more than half of their patients had an acute coronary syndrome, with a direct effect on prognosis, probably influencing the results. A small study of 269 patients undergoing elective stent implantation showed a significant association between postprocedural troponin T and the

combined endpoint of death, myocardial infarction and coronary bypass grafting during follow-up [9], which was confirmed by three other small studies focusing on MACE [10,11,19]. Another study however, could not confirm this relation in 1129 patients during 8-months follow-up [12]. In a meta-analysis of 7 small studies, there was a significant association between troponins (I and T) and the combined endpoint of myocardial infarction/death, but not between increased troponin and MACE [13]. Two other studies could not demonstrate an association between postprocedural troponin I rise and mortality in 1-year follow-up [14,15]. In patients with chronic renal failure, but not on dialysis, postprocedural troponin I rise seems to be strongly associated with mortality as well as with MACE in follow-up [20].

*Study limitations*

Our study has several limitations. First, the number of patients was relatively small and the follow-up period relatively short. However, most previous studies had an even smaller sample size and also a short follow-up period. Second, the primary combined endpoint included five different endpoints. However, a study in such a low-risk population with only endpoint death or myocardial infarction should include thousands of patients to be powered. Third, there was no detailed description of lesion morphology and angiographic complications of the percutaneous coronary intervention such as side branch occlusion. Fourth, the use of glycoprotein IIb/IIIa receptor inhibitors was low, as could be expected in this low risk population [36]. Fifth, although our study is a prospective, non-randomised registry, there was no routine angiographic follow-up. Sixth, although the used cut-off value of 0.05 ng/ml for troponin T is commonly used, cut-off values of 0.01 and 0.03 ng/ml might be used as well [37,38]. However, additional analyses with 0.03 ng/ml as cut-off value did not change the conclusions, and, as mentioned earlier, 0.05 ng/ml was pre-specified in the protocol and therefore used in the final analysis. Finally, the blood samples after percutaneous coronary intervention were taken only once, with possibly underestimating the total troponin T release.

*Implications*

The recently revised European guidelines for percutaneous coronary intervention do not recommend the use of troponin T after percutaneous coronary intervention [39]. However, the recommendation in these guidelines seems to be based on only four studies, including one meta-analysis which included studies that were not yet published [13]. According to the also recently revised ACC/AHA

guidelines, most patients can be safely discharged within 24 h after an elective, uncomplicated percutaneous coronary intervention [40]. Biochemical evidence of periprocedural myocardial infarction is defined by rise of CK-MB or troponin I or T after percutaneous coronary intervention. Determining these markers is recommended for patients with signs or symptoms suggestive of myocardial infarction or angiographic evidence of complications, although routine measurement of these cardiac biomarkers seems to be reasonable 8 to 12 hours after the procedure, according to these American guidelines.
Our study suggests that troponin T is better to identify patients at risk for future cardiac adverse events when compared to creatine kinase.

*Conclusion*
Troponin T predicts better than creatine kinase future cardiac events in patients undergoing elective percutaneous coronary intervention. Whether more intensive monitoring and treatment of patients with increased troponin T after percutaneous coronary intervention will improve their prognosis remains to be determined.

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# Chapter 3

# Pre-treatment with clopidogrel and postprocedure troponin elevation after elective percutaneous coronary intervention

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**ABSTRACT**

**Background:** Elevated troponin after elective percutaneous coronary intervention (PCI) has been associated with a worse prognosis. Pre-treatment with clopidogrel may be beneficial in patients undergoing PCI. Therefore, a prospective observational study was conducted to address the potential role of clopidogrel in reducing troponin release after elective PCI.

**Methods:** Troponin T was measured 12 hours after elective PCI in 656 patients without elevated troponin before PCI. To assess the independent association between pre-treatment with clopidogrel and increased troponin, multivariate analyses were performed.

**Results:** Mean age of the 656 patients was 63.5 years (SD 10.2), 194 patients (30%) were female and 114 patients (17.4%) had diabetes. In 217 patients (33%) troponin was increased after PCI. Of the 330 patients who were not pre-treated with clopidogrel, 118 patients (34%) had increased troponin after the PCI compared to 99 patients (30%) of the 326 patients who were treated with clopidogrel longer than 24 hours before the procedure (p=0.14). Stratified analyses showed that patients with older age (p=0.03), previous PCI (p=0.013), angina CCS 4 (p=0.03) and multivessel disease (p=0.04) had a significantly lower risk of troponin increase after pre-treatment with clopidogrel compared to patients without pre-treatment. After adjusting for differences in the other variables, patients who were pre-treated with clopidogrel had a significant lower risk of post-PCI increase of troponin T (odds ratio 0.69, 95% confidence interval 0.49-0.99).

**Conclusion:** Pre-treatment with clopidogrel is associated with a significantly lower incidence of increased troponin after elective PCI. Combined with results of other studies, pre-treatment should be advised in patients waiting for elective PCI.

## Introduction

Intensive antiplatelet therapy is the cornerstone of pharmacological treatment of patients undergoing percutaneous coronary intervention (PCI) and may consist of aspirin, GP IIb/IIIa inhibitors and the ADP antagonist clopidogrel [1-3]. In addition to postprocedural treatment with clopidogrel, treatment with clopidogrel before PCI may also be beneficial [4-8], although a small study could not confirm this observation [9]. However, these data are based on selected patients included in randomised clinical trials, and the results may be not comparable to these observed in daily practice.

Postprocedural rise of troponin levels has been associated with an increased incidence of cardiac events during follow-up [10,11]. Troponin release occurs in approximately 30% of patients and has been related to complications during the procedure, including sapheneous vein graft interventions, multistent use, glycoprotein IIb/IIIa use, and a history of hypercholesterolemia [12].

We studied the potential association between pre-treatment with clopidogrel on the postprocedural troponin levels in consecutive, unselected patients undergoing elective PCI in daily practice.

## Methods

*Study population*

A prospective, observational study was performed. The patient cohort included unselected patients who underwent elective PCI between June 2002 and August 2003 in a single centre (Isala klinieken, Zwolle, the Netherlands). All patients had symptomatic coronary artery disease with objective signs of ischemia.

Patients with PCI for ST-segment elevation MI were excluded, as well as patients with urgent PCI for severe unstable coronary artery disease. The remaining patients consisted of outpatients with stable angina and patients referred from other hospitals with more severe or progressive angina. At the time when the study was performed, routine use of clopidogrel before PCI was not advised, leaving it at the discretion of the referring treating cardiologist. Use of clopidogrel before PCI was defined as starting clopidogrel more than 24 hours before PCI. All patients who were not treated with clopidogrel before the PCI received a loading dose of 300 mg clopidogrel just before the procedure. All patients were treated with clopidogrel 75 mg once daily for at least 28 days after the procedure.

*Procedure and laboratory testing*

Routine care before and after the procedure was undertaken for all patients, including the preprocedural use of aspirin and a bolus of intravenous heparin (5000 U) at the beginning of the procedure. Use of stents or GP IIb-IIIa inhibitors was left at the discretion of the interventional cardiologist.

A blood sample was routinely obtained from all patients just before the interventional procedure in the catheterisation room. The second sample was taken the day after, 12-16 hours after the procedure. All samples were prepared and stored locally in our core laboratory at -70°C until analysis.

Troponin T was analysed using the third generation troponin T test (Roche diagnostics, Mannheim, Germany) with a threshold of 0.01 ng/ml, which was used in our study as the cut-off value.

*Statistical analysis*

Differences in baseline characteristics between patients with and without clopidogrel pre-treatment and those with and without increased troponin after the PCI procedure were compared by means of the Chi-square test or Fisher's exact test for proportions and Student's t test for continuous variables.

Multivariate analysis (logistic regression analysis) was performed to assess the independent association between pre-treatment with clopidogrel and increased troponin level after the procedure. A two-tailed p value of $<0.05$ was considered statistically significant. All analyses were performed with SPSS statistical software (SPSS Inc., Chicago, Illinois).

**Results**

Of 745 patients enrolled in the study, data on treatment with clopidogrel before admission was available in 714 patients (96%). Of these 714 patients, a total of 656 patients (92%) had no elevated troponin T (<0.01 ng/ml) before the PCI and these patients represent the final study group. Mean age was 63.5 years (SD 10.2), 194 patients (30%) were female and 114 patients (17.4%) had diabetes. Multivessel disease was present in 314 patients (48%), and 101 patients (15%) had CCS class 4 angina.

In a total of 326 patients (50%), clopidogrel was started 24 hours or more before PCI. Differences between patients with and without pre-treatment with clopidogrel are summarised in table 1. Patients who were pre-treated with clopidogrel were younger, were more often waiting in a referring hospital for the PCI and had less often diabetes or a history of PCI. Patients with angina class 4 more often had clopidogrel started 24 hours or more before the PCI.

**Table 1.** Baseline clinical and target lesion characteristics of 656 patients with elective PCI, data on preprocedure start of clopidogrel and without increased troponin T before the procedure.

| | Clopidogrel Pretreatment (n=326) | No Clopidogrel Pretreatment (n=330) | P |
|---|---|---|---|
| Age, yrs (sd) | 62.6 (±10.6) | 64.4 (±9.7) | 0.02 |
| Female | 105 (32) | 89 (27) | 0.14 |
| Waiting in hospital for PCI | 47 (15) | 29 (9) | 0.02 |
| Risk factors | | | |
| Diabetes mellitus | 46 (14) | 68 (21) | 0.03 |
| Hypercholesterolemia | 182 (71) | 186 (66) | 0.23 |
| Smoking | 121 (38) | 88 (28) | 0.01 |
| Family history of coronary artery disease | 113 (38) | 123 (40) | 0.54 |
| Medical history | | | |
| Myocardial infarction | 144 (44) | 139 (42) | 0.60 |
| PCI | 69 (21) | 103 (31) | 0.004 |
| Coronary bypass grafting | 28 (9) | 44 (13) | 0.05 |
| Stroke | 26 (8) | 21 (6) | 0.42 |
| Use of stent | 235 (72) | 227 (69) | 0.35 |
| Angina CCS 4 | 81 (25) | 20 (6) | 0.001 |
| Multivessel Disease | 155 (48) | 159 (48) | 0.87 |
| RCA | 98 (30) | 81 (25) | 0.16 |
| LAD | 155 (48) | 128 (39) | 0.02 |
| Multivessel PCI | 63 (19) | 69 (21) | 0.61 |

All in n (%), except when is indicated else

In 217 patients (33%), troponin was increased after the PCI. Differences between patients with and without increased troponin after the PCI are shown in table 2. Patients with increased troponin more often had multivessel disease, all other variables were not significantly different. Of the 330 patients who were not pre-treated with clopidogrel, 118 patients (34%) had increased troponin after the PCI compared to 99 patients (30%) of the 326 patients who were treated longer than 24 hours before the PCI with clopidogrel (p=0.14). During hospital admission, there were no patients with intracerebral hemorrhage or signs of stroke.

**Table 2.** Predictors of increased troponin (>0.01 ng/ml) after elective PCI in 656 patients without increased troponin (<0.01ng/ml) before the PCI and with data on clopidogrel use.

| | Troponin not increased (n=439) | Troponin increased (n=217) | P |
|---|---|---|---|
| Age, yrs (sd) | 63.0 (±9.9) | 64.3 (±10.7) | 0.13 |
| Female | 127 (29) | 67 (31) | 0.61 |
| Risk factors | | | |
| Diabetes mellitus | 37 (17) | 77 (18) | 0.87 |
| Hypercholesterolemia | 248 (68) | 116 (68) | 0.98 |
| Smoking | 139 (33) | 70 (33) | 0.86 |
| Family history of coronary artery disease | 161 (39) | 75 (38) | 0.66 |
| Multivessel disease | 193 (44) | 121 (56) | 0.004 |
| Medical history | | | |
| Myocardial infarction | 187 (43) | 96 (44) | 0.67 |
| PCI | 124 (28) | 48 (22) | 0.10 |
| Coronary bypass grafting | 53 (12) | 19 (9) | 0.20 |
| Stroke | 26 (6) | 21 (10) | 0.08 |
| PCI | | | |
| RCA | 129 (29) | 50 (23) | 0.09 |
| LAD | 187 (43) | 96 (44) | 0.69 |
| Multivessel PCI | 69 (16) | 63 (29) | 0.001 |
| Clopidogrel pre-treatment | 227 (52) | 99 (46) | 0.14 |
| GP IIb/IIIa inhibitor pre-treatment | 27 (6) | 9 (4) | 0.29 |
| Stent | 308 (70) | 154 (72) | 0.70 |
| Angina CCS4 | 63 (14) | 38 (18) | 0.29 |

All in n (%), except when is indicated else

A stratified analysis was performed to assess whether specific subgroups had more benefit of pre-treatment with clopidogrel (Figure 1). There was a consistent reduction of the risk of troponin elevation after PCI after pre-treatment with clopidogrel in all subgroups. It was demonstrated that particularly patients at older age (p=0.03), with previous PCI (p=0.013), with angina CCS 4 (p=0.03) and multivessel disease (p=0.04) had a significantly lower risk of troponin increase after pre-treatment with clopidogrel.

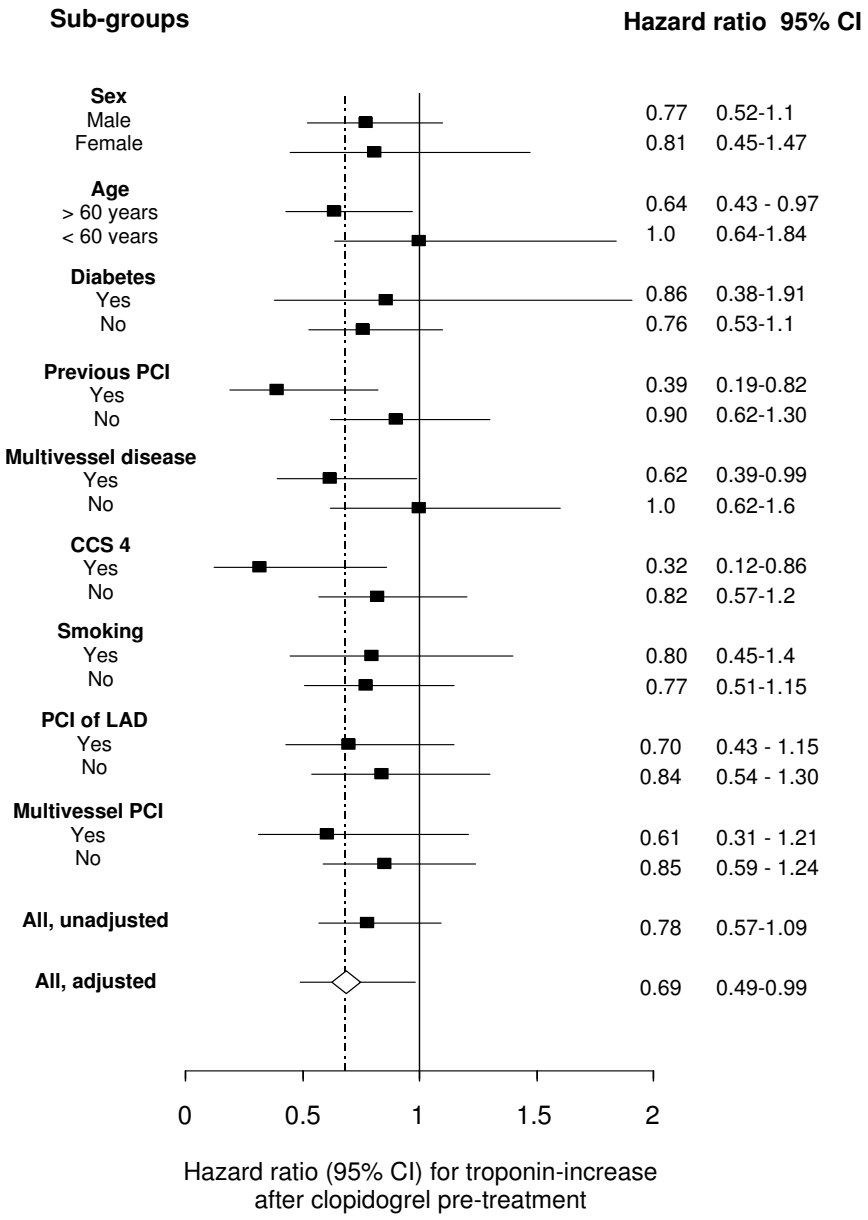


**Figure 1.** Stratified analyses of risk of increased troponin after pre-treatment with clopidogrel in several subgroups (no pre-treatment is the reference group).

Since there were several significant differences between patients with and without pre-treatment with clopidogrel, multivariate analysis was performed to assess the independent association between pre-treatment with clopidogrel and troponin increase after the PCI. The results of multivariate analyses are presented in table 3. After adjusting for differences in the other variables, patients who were pre-treated with clopidogrel had a significant lower risk of post-PCI increase of troponin T (odds ratio 0.69, 95% confidence interval 0.49-0.99; p=0.04).

**Table 3.** Predictors of increased troponin (>0.01 ng/ml) after elective PCI in 656 patients without increased troponin (<0.01 ng/ml) before the PCI and with data on clopidogrel use, multivariate analysis.

| Variable | Odds ratio | 95% Confidence Interval | P |
|---|---|---|---|
| Age (/year) | 1.01 | 0.99-1.03 | 0.30 |
| Male gender | 0.96 | 0.66-1.41 | 0.85 |
| Diabetes | 0.89 | 0.56-1.41 | 0.62 |
| Previous PCI | 0.67 | 0.44-1.0 | 0.05 |
| Angina CCS 4 | 1.37 | 0.85-2.2 | 0.20 |
| Smoking | 1.15 | 0.78-1.70 | 0.48 |
| Multivessel disease | 1.46 | 1.0-2.1 | 0.04 |
| PCI of LAD | 1.24 | 0.87-1.76 | 0.24 |
| Multivessel PCI | 2.07 | 1.37-3.15 | 0.001 |
| Clopidogrel pretreatment | 0.69 | 0.49-0.99 | 0.04 |

## Discussion

Our study shows that in patients undergoing elective PCI, pre-treatment with clopidogrel was associated with a decreased risk of elevated troponin after the PCI. Several subgroups, including older age and those with multivessel disease, CCS class 4 angina or previous PCI had particular benefit of pre-treatment with clopidogrel.

The results of our study are consistent with observations from randomised trials. In the TARGET study, 4809 patients undergoing elective or urgent PCI were randomised to tirofiban or abciximab. A sub-analysis of patients with clopidogrel pre-treatment showed a lower incidence of cardiovascular events at 30 days and a lower mortality at 1 year [4]. The beneficial effect of pre-treatment with clopidogrel was also suggested in the PCI-CURE study, involving patients with an acute coronary syndrome without ST-segment elevation [5]. Furthermore, Berglund et al found a significant beneficial effect of clopidogrel pre-treatment in

reducing myocardial infarction and percutaneous reintervention after PCI. However, this concerned a non-randomised study in patients with unstable coronary syndromes [6].

The Clopidogrel for the Reduction of Events During Observation (CREDO) study, including 2116 patients, has shown that pre-treatment with clopidogrel has no beneficial effects. However, when subgroup analysis was performed with regard to duration of pre-treatment, its seemed that a longer duration of pre-treatment (>6 hours) is beneficial [7]. In ISAR-REACT there was no difference in the 30 days outcome between those pre-treated with clopidogrel 2-3 hours versus >12 hours. However, this trial had many exclusion criteria, resulting in inclusion of a very low risk population [8]. In another small study in 203 patients undergoing elective stent implantation, clopidogrel pre-treatment of 3 days did reduce neither the post-procedural release of troponin I and CK-MB nor cardiovascular events during 6 months follow-up [9].

Several studies have been conducted to address platelet aggregation inhibition and the timing of clopidogrel administration. It has been shown that a 300 mg clopidogrel loading dose, given 3 to 24 hours before stenting, is associated with a better platelets inhibition and a reduced poststent activity, when compared to a 75 mg dose given at the time of the procedure [13]. In a non-randomized, observational study, the effects of a 600 mg loading dose of clopidogrel at different time periods before elective PCI were studied [14]. After 2 hours, the level of platelet aggregation and the surface expression of P-selectin and activated glycoprotein IIb/IIIa did not further change with time after clopidogrel administration. Furthermore, they could not demonstrate any difference in clinical endpoints at 30 days. The large inter-individual variability in the platelet inhibitory response from clopidogrel [15] and the inclusion of low-risk patients, in small studies, may possibly explain the failure to show significant differences between achieved platelet aggregation in patients with or without pre-treatment with clopidogrel [16,17].

Apart from direct effects on platelet aggregation, clopidogrel may also have effects on the inflammatory response. It has been demonstrated that clopidogrel pre-treatment (longer than 24 hours before PCI) reduces platelet inflammatory marker expression in patients undergoing PCI compared to patients without pre-treatment [18]. Although a high loading dose of 600 mg clopidogrel may optimise platelet inhibitory effects early after intervention and may provide a more effective protection against early thrombotic complications [14,19], the question remains

whether this has comparable effect on the inflammatory response. Therefore, further research on this topic might be necessary.

Our study confirms earlier reports that a relatively high number of patients with elective PCI develop elevated troponin, even if the procedure is successful and uncomplicated. These elevations, even when minor, have been associated with an increased incidence of repeat revascularisations, acute myocardial infarction and death [10,20-23].

*Limitations*

Our study has several limitations. We present data from a prospective, observational study, without randomisation. Because pre-treatment with clopidogrel was left to the discretion of the cardiologist, the decision for pre-treatment may have introduced confounding. Probably, patients who were pre-treated with clopidogrel may represent a more unstable group. It is therefore not surprising that significant differences could be observed between patients with and without pre-treatment with clopidogrel (table 1). Nevertheless, after correction for these confounding variables, a significantly lower risk of post PCI troponin rise was demonstrated in patients pre-treated with clopidogrel. We did not perform a sample size calculation. Because the sample size of the study was not very large, the number of patients in the subgroups were small. The study was not designed and powered to assess potential association between clopidogrel pre-treatment, troponin release and outcome. With our sample size and a low-risk population, a significant difference in events during follow-up can not be expected. Another limitation is that we had neither data on levels of platelet aggregation inhibition nor data on angiographic causes of troponin elevation, including loss of side branches, distal embolization or no-reflow. Also, we didn't collect data on bleeding complications (although there were no patients with intracerebral hemorrhage).

*Conclusion*

Clopidogrel pre-treatment before elective PCI is associated with a decreased risk of post-PCI troponin rise. Combined with results of several randomised trials, pre-treatment with clopidogrel before elective PCI should be strongly considered.

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# Chapter 4

# Troponin T elevation and prognosis after multivessel compared to single vessel elective percutaneous coronary intervention

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**ABSTRACT**

**Background:** Although techniques of percutaneous coronary interventions (PCI) have improved, patients with PCI of more vessels may still have an increased risk. We performed a prospective observational study evaluating the differences between multivessel and single-vessel procedures according to postprocedural troponin T (TnT) elevation and events during follow-up.

**Methods:** The study included 713 patients without elevated TnT (<0.05 ng/ml) before PCI. Primary endpoint was the combined endpoint of death, myocardial infarction, stroke, repeat coronary angiography and re-admission for anginal symptoms during the mean follow-up of 10.9 months.

**Results:** TnT after PCI was elevated in 150 patients (21%) and was significantly associated with an increased incidence of the primary endpoint (RR 1.55 95% CI 1.01-2.38). PCI of more than one vessel was performed in 146 patients (20%). These patients more often had increased TnT levels after the procedure (31.5% vs 18.3%, p=0.001) and an increased incidence of the primary endpoint during follow-up (28% vs 19%, p=0.01). After multivariable analysis, multivessel PCI was a statistically significant predictor of postprocedural TnT increase (OR 1.90, 95% CI 1.17-3.06). Multivessel PCI was also associated with an increased risk of the primary endpoint (OR 1.73, 95% CI 1.18-2.52), but after adjusting for multivessel disease this association was not statistically significant (OR 1.42, 95% CI 0.92-2.19).

**Conclusion:** Elective PCI of more vessels in one session is, in comparison with single-vessel PCI, more often associated with postprocedural troponin T rise and a (non-significantly) higher incidence of cardiac events during follow-up. Whether staged PCI is associated with less morbidity has to be assessed.

## Introduction

During the last decade, percutaneous coronary intervention (PCI) has been improved [1]. Use of (drug eluting) stents has decreased the occurrence of re-stenosis. Furthermore, PCI is now often combined with diagnostic coronary angiography in one procedure [2,3]. Another development is performing multivessel PCI in one session. Although it was not confirmed by a recently published registry [4], randomised trials suggested that in most patients with multivessel disease, PCI is comparable to coronary artery bypass grafting (CABG) according to mortality and myocardial infarction (MI) in follow-up [5]. Performing more interventions in one procedure may be faster and more convenient than staged procedures. Although one study suggests that this one-session strategy might be more harmful, there are only few data on this issue [6].
After elective PCI, up to 30% of patients develop elevated cardiac specific troponin T (TnT) even when the procedure is considered successful and uncomplicated. Such elevations of TnT have been associated with an increased incidence of future cardiac events [7-11].
The current prospective study was designed to evaluate the effect of multivessel PCI versus single vessel PCI on the incidence of troponin T (TnT) elevation after elective PCI and the occurrence of cardiac events during follow-up.

## Materials and Methods

*Study population*
It concerns a prospective, observational study [11]. The patient cohort included unselected patients who underwent elective PCI between June 2002 and August 2003 in Isala klinieken, Zwolle, the Netherlands. All patients had symptomatic coronary artery disease with objective evidence of ischemia.
Patients with single vessel as well as patients with multivessel disease were included. Multivessel disease was defined as more than 50% stenosis in two or more major coronary arteries. If in patients with multivessel disease, culprit lesion interventions only or multivessel interventions for multiple lesions in more than one vessel were indicated, depended of the decision of the cardiologist and cardiac surgeon (heart team). Patients with acute coronary syndrome (ACS) were excluded.

*Procedure and laboratory testing*

All PCI procedures were performed according to the standard protocol. Routine care before and after the procedure was undertaken for all patients, including preprocedural use of aspirin and a bolus of intravenous heparin (5000 U) at the beginning of the procedure. Patients not on clopidogrel (approximately 50%) received a loading dose of 300 mg clopidogrel just before the procedure. Postprocedure, all patients were treated with clopidogrel 75 mg once daily for at least 28 days. Use of GP IIb-IIIa inhibitors or stents was at the discretion of the interventional cardiologist. At the time the study was performed, the use of drug eluting stents was less than 10%.

A blood sample was routinely obtained from all patients just before the interventional procedure in the catheterisation room. The second sample was taken the day after, approximately 12 hours after the procedure. All samples were prepared and stored locally in our core laboratory at -70°C until analysed. The medical practitioners were blinded for the results of this analysis.

TnT was analyzed using the third generation troponin T test (Roche diagnostics, Mannheim, Germany) with a threshold of 0.01 ng/ml. Although the 99st percentile of normal TnT may be as low as 0.01 ng/ml, in accordance with other recent studies we used 0.05 ng/ml as cut off value [12-14].

*Endpoints*

The primary endpoint was the combined incidence of re-admission because of angina, repeat coronary angiography, repeat revascularisation, MI, stroke and death. The second primary endpoint was TnT elevation after PCI. Clinical outcomes were obtained at least 30 days after PCI by telephone interviews with the patient, their relatives or eventually their cardiologist or primary physician. Information on clinical events was noted using a standardised format. All clinical events were obtained from the medical files. New onset of Q waves or CK and CK-MB above cut off values was used as definition for MI during follow-up. All deaths during follow-up were considered of cardiac cause, unless a noncardiac cause was identified.

*Statistical analysis*

All analyses were performed with SPSS statistical software (SPSS Inc., Chicago, Illinois). Group comparisons were done by the chi-square test for proportions and Student t test for continuous variables. Multivariable analysis by logistic regression were performed to asses the independent association between

multivessel PCI and increased TnT after the PCI. Multivariate Cox' proportional-hazards regression analysis was applied to describe the independent relation between multivessel PCI and the occurrence of the primary endpoint during follow-up. A probability value of $p < 0.05$ was considered significant.

## Results

During the enrolment period, 745 patients were screened for our study. Of these 745 patients, a total of 713 patients (96%) had no elevated TnT (<0.05 ng/ml) before the PCI, representing the final study group. Mean age was 64 years (range 35-87 years), 211 patients (30%) were female, 127 patients (18%) had diabetes and 111 patients (16%) had angina with CCS class 4. A total of 501 patients (70%) were treated with a stent. Multivessel disease was present in 381 patients (53%) which was documented before the PCI procedure in 344 patients (90%). PCI of more than one vessel was performed in 146 patients (20%). Differences between patients with multivessel PCI and PCI of one vessel are summarized in table 1. It is shown that there are no major differences between the two patient groups.

**Table 1.** Characteristics of 713 pts; multivessel procedure versus single-vessel procedure.

| Variables | Multivessel PCI (n=146) | Single-vessel PCI (n=567) | P |
|---|---|---|---|
| Age, yrs (sd) | 64.1 (±10.3) | 63.4 (±10.4) | 0.46 |
| Female | 45 (31) | 166 (29) | 0.72 |
| Risk factors | | | |
| Diabetes mellitus | 27 (18) | 100 (18) | 0.82 |
| Hypercholesterolemia | 84 (58) | 314 (55) | 0.11 |
| Smoking | 42 (29) | 188 (33) | 0.31 |
| Hypertension | 69 (47) | 242 (43) | 0.15 |
| Family history of CAD | 60 (41) | 190 (34) | 0.08 |
| Angina CCS4 before PCI | 23 (16) | 88 (16) | 0.95 |
| Medical history | | | |
| Myocardial infarction | 73 (50) | 246 (43) | 0.16 |
| PCI | 45 (31) | 144 (25) | 0.19 |
| CABG | 11 (8) | 73 (13) | 0.07 |
| Stroke | 14 (10) | 37 (7) | 0.20 |
| Following PCI | | | |
| Death | 0 | 9 (2) | 0.13 |
| Combined endpoint | 39 (27) | 100 (18) | 0.014 |
| Postprocedural troponin elevation | 46 (32) | 104 (18) | 0.001 |

All in n (%), except when is indicated else

Baseline characteristics of the 381 patients in the subgroup with multivessel disease did not differ essentially from the entire study group of 713 patients. There were only few differences between patients undergoing multivessel and single vessel PCI in this subgroup. Patients with previous CABG less often had multivessel PCI (8% vs 24%, p <0.001), whereas previous PCI (31% vs 26%) and MI in history (50% vs 49%) were not significantly different. Furthermore, patients with PCI of the right coronary artery significantly more often had multivessel PCI (37% vs 26%, p =0.03).

In patients with multivessel disease, postprocedural troponin elevation occurred significantly more often in patients undergoing multivessel PCI compared to single vessel PCI (32% vs 20%, p =0.008). However, multivessel PCI was neither significantly associated with mortality in follow-up, nor with the primary combined clinical endpoint in this selected group (27% vs 21%, p =0.19).

**Table 2.** Baseline characteristics of 713 pts according to troponin increase (>0.05 ng/ml) after elective PCI.

| Variables | Troponin not increased (n=563) | Troponin increased (n=150) | P |
|---|---|---|---|
| Age, yrs (sd) | 63.5 (±10) | 63.7 (±11) | 0.84 |
| Female | 172 (31) | 39 (26) | 0.28 |
| Risk factors | | | |
| Diabetes mellitus | 108 (19) | 19 (13) | 0.06 |
| Hypercholesterolemia | 316 (69) | 82 (68) | 0.94 |
| Smoking | 179 (33) | 51 (35) | 0.61 |
| Hypertension | 249 (49) | 62 (48) | 0.80 |
| Family history of CAD | 195 (37) | 55 (40) | 0.59 |
| Multivessel disease | 289(51) | 92 (61) | 0.03 |
| Medical history | | | |
| Myocardial infarction | 249 (44) | 70 (47) | 0.56 |
| PCI | 148 (26) | 41 (27) | 0.81 |
| CABG | 68 (12) | 16 (11) | 0.63 |
| Stroke | 38 (6.7) | 13 (8.7) | 0.42 |
| PCI | | | |
| RCA | 165 (29) | 35 (23) | 0.15 |
| LAD | 239 (43) | 60 (40) | 0.59 |
| Multivessel PCI | 100 (18) | 46 (31) | 0.001 |
| Stent | 395 (70) | 106 (72) | 0.73 |
| Angina CCS4 | 81 (14) | 30 (20) | 0.09 |

All in n (%), except when is indicated else

TnT was elevated after the PCI in 150 patients of the total study population (21%). All baseline variables according to elevated troponin after the PCI are shown in table 2. Multivessel disease and multivessel PCI were both significantly associated with increased TnT rise after PCI (p=0.001). The unadjusted odds ratio (OR) for increased TnT after multivessel PCI was 2.1 (95% CI 1.4-3.1). After multivariable analyses, adjusting for age, gender, diabetes, CCS classification and multivessel disease, multivessel PCI (OR 1.9, 95% CI 1.17-3.06), but not multivessel disease (OR 1.17, 95% CI 0.76-1.8) was significantly associated with increased TnT after the PCI.

30-days follow-up was available in all patients, mean total follow-up was 10.9 months (SD 10.6). Long-term mortality was low (1.3%) and associated with neither multivessel PCI nor TnT elevation after PCI. The occurrence of the combined endpoint death and/or MI in follow-up was also low and not related to troponin release (2.1% (12/563) for patients with non-elevated troponin vs 4.0% (6/150) for patients with elevated troponin, NS). Patients with multivessel PCI had more often recurrent PCI (19 patients, 13.0%) compared to single vessel PCI (39 patients, 6.9%, p =0.016).
During the follow-up period, the primary combined endpoint was observed in 139 patients (19.5 %): 9 patients died (2 of noncardiac, 7 of cardiac or unknown cause), 8 patients had a MI and 64 underwent recurrent revascularisation (49 PCI, 6 CABG, 9 PCI and CABG). Furthermore, 7 patients had a stroke, 36 patients underwent re-angiography and another 15 patients were re-admitted for anginal symptoms.

Differences between patients with and without a primary endpoint during the follow-up period are shown in table 3. An increased risk of occurrence of the primary endpoint was observed in patients with diabetes, in patients with a PCI or CABG in history, in patients with multivessel disease and in patients with an increased TnT after PCI. Also patients with PCI of more vessels had significantly more events during follow-up, with the unadjusted odds ratio 1.7 (95% CI 1.2-2.5). After adjusting for differences in age, gender, diabetes and CCS classification, multivessel PCI had an increased incidence of the primary endpoint, OR 1.73, 95% CI 1.18-2.52. However, if multivessel disease was also included in the multivariable model, the association was not statistically significant, OR 1.42 (95% CI 0.92-2.19).

**Table 3.** Baseline characteristics of 713 pts according to cardiac events[1] during follow-up.

| Variables | Patients with events (n=139) | Patients without events (n=574) | P |
|---|---|---|---|
| Age, yrs (sd) | 64.9 (±10.3) | 64.9 (±10.3) | 0.8 |
| Female | 46 (33) | 165 (29) | 0.31 |
| Risk factors | | | |
| Diabetes mellitus | 40 (29) | 87 (15) | 0.01 |
| Hypercholesterolemia | 85 (72) | 313 (68) | 0.37 |
| Smoking | 39 (29) | 191 (34) | 0.24 |
| Hypertension | 65 (51) | 246 (49) | 0.59 |
| Family history of CAD | 50 (39) | 200 (38) | 0.70 |
| Multivessel disease | 88 (63) | 293 (51) | 0.009 |
| Medical history | | | |
| Myocardial infarction | 67 (48) | 252 (44) | 0.38 |
| PCI | 61 (44) | 128 (22) | 0.001 |
| CABG | 26 (19) | 58 (10) | 0.005 |
| Stroke | 4 (3) | 47 (8.2) | 0.03 |
| PCI | | | |
| RCA | 39 (28) | 161 (28) | 1.0 |
| LAD | 54 (39) | 245 (43) | 0.41 |
| Multivessel PCI | 39 (28) | 107 (19) | 0.01 |
| Stent | 97 (70) | 404 (71) | 0.85 |
| CCS4 | 20 (14) | 91 (16) | 0.67 |
| Tropinin increase after PCI | 38 (27) | 112 (20) | 0.04 |

All in n (%), except when is indicated else

[1]Primary endpoint: re-admission, repeat coronary angiography, repeat PCI, CABG, MI, stroke and death

## Discussion

Multivessel PCI was, in comparison with single vessel procedure, significantly associated with more often postprocedural TnT release. Multivessel PCI was also associated with an increased incidence of cardiac events during the follow-up period, but this could in part be explained by multivessel disease itself. Mortality in this low-risk population was low and not associated with multivessel PCI.

In patients undergoing elective multivessel PCI, there are conflicting results about the safety and long term results. One study reported similar clinical outcomes for patients undergoing multivessel PCI when compared with patients undergoing single vessel PCI [15]. Others report comparable events in follow-up for both groups, except for re-PCI, occurring more frequent in patients undergoing multivessel PCI [16,17]. IJsselmuiden et al randomized 219 patients with

multivessel disease to complete versus culprit vessel PCI, resulting in similar major adverse cardiac events at follow-up and similar total costs after one year in the two groups [18]. Recently, it was observed that in patients planned for multivessel PCI, interventions of hemodynamically non-significant stenoses can be safely deferred, based on fractional flow reserve (FFR) measurements [19].

In an analysis of the TARGET study, multivessel PCI was, when compared with single vessel PCI, more often associated with events in follow-up, primarily due to an increase in periprocedural MI [20]. However, one important, but not reported baseline characteristic was the presence of multivessel disease, which might have influenced the results. Other studies reported a relation between periprocedural myocardial injury and multivessel PCI [21,22]. Only one study compared staging of multivessel PCI with the one-procedure approach [6], with a non-significant trend that patients in the staged group had less cardiac events ($p=0.08$). This trend was mainly the result of a lower need for reinterventions. In the setting of ST-elevation MI, it is yet unknown whether treatment of only the infarct-related-artery is superior to multivessel intervention [23,24].

Troponin release after PCI occurs in approximately 30% of patients and has been related to several patient-related factors, including multivessel coronary artery disease, older age, interventions of de-novo lesions, sapheneous vein graft interventions and complex lesions [22]. Also procedure-related factors may be of importance, like the no-reflow phenomenon, distal embolization and side branch occlusion [25].

Since troponin release is associated with several procedure-related factors, it is not surprising that performing PCI in more than one vessel during the same procedure is (also in our study) associated with more often troponin release after PCI. This can be explained by several mechanisms: First, it has been demonstrated that postprocedural enzyme release relates to intraprocedural reduction of plaque volume, pointing towards the significance of atheroembolization in peri-procedural myocardial injury [26]. Therefore, PCI of more vessels, reducing more plaque volume, may result in more often significant enzyme release. Second, in vivo plaque disruption by PCI causes shedding of potent biofactors such as tissue factor into the coronary circulation, leading to microvascular thrombosis and no-reflow [27]. This thrombogenic state can influence the result of additional PCI procedures in the same setting. Third, as

PCI directly result in activation of the sympathetic nervous system, which in turn result in diffuse vasoconstriction [28], every additional PCI performed can result in extra troponin release.

Staging of the PCI by performing first a single vessel procedure, followed weeks or months later by an additional procedure might result in less troponin release and less cardiac events, although this has not been proven yet. More often use of FFR may prevent unnecessary PCI.

*Limitations*

The presented study has some limitations. First, it concerns an observational study and differences between patients with and without multivessel disease could have influenced the results. Second, because mortality and MI in this group are low, the primary combined endpoint consisted of a number of different endpoints. These endpoints may be considered as weak, but an important reason for performing elective PCI is to improve quality of life. Knowing the low risk of events after elective PCI in stable patients and realising re-admission and repeat angiography are “events” in the patients point of view, these two endpoints were also included in the primary combined endpoint. Third, the number of patients was relatively small. Together with the low mortality during follow-up, no association could be demonstrated between multivessel PCI, TnT release and mortality, although it is not excluded that this relation does exist. As a consequence of the relatively low number of patients and particularly the low event rate, additional subgroup analyses, for example stratifying to the magnitude of troponin release, were not possible. Fourth, the use of drug eluting stents was low. Although this probably will not have influenced data on troponin release, it might have influenced the follow-up data, especially the need for recurrent revascularization. Fifth, approximately 50% of our patients were not on clopidogrel before the PCI and received the drug just before the procedure. This could have influenced the results, because the protective effect of clopidogrel is stronger when it is given several hours or more before the procedure [29]. Sixth, no routine angiographic follow-up was available for our patient cohort. Finally, as a routine electrocardiogram was not collected in the follow-up period, the number of MI in follow-up could have been underestimated.

*Conclusion*

A multivessel PCI procedure is, when compared to single vessel procedure, associated with more TnT release. Furthermore, there is a trend towards a higher incidence of cardiac events during follow-up after a multivessel procedure. Whether a staged approach in patients with multivessel disease is associated with less events during follow-up has to be assessed.

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# Chapter 5

# Prognostic value of troponin after elective percutaneous coronary intervention: A Meta-Analysis

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**ABSTRACT**

**Background:** Although the prognostic importance of troponin in patients with an acute coronary syndrome is clear, the significance of troponin elevation after elective percutaneous coronary intervention (PCI) is subject of debate. However, most studies up to now had a small sample size and insufficient events during follow-up.

**Methods:** Electronic and manual searches were performed of studies reporting on prognosis of troponin after elective PCI. A meta-analysis was done of all suitable studies, with death in follow-up as primary endpoint and the combination of death or non-fatal myocardial infarction in follow-up as secondary endpoint.

**Results:** 20 studies involving 15,581 patients were included. These studies were published between 1998 and 2007. Overall, troponin was elevated after elective PCI in 32.9% of patients. The follow-up period varied between 3 and 67 months (mean 16.3). Increased mortality was significantly associated with troponin elevation after PCI (4.4% vs 3.3%, p =0.001; OR 1.35). Furthermore, the combined endpoint of mortality or non-fatal myocardial infarction occurred also more often in patients with post-procedural troponin elevation (8.1% vs 5.2%, p <0.001; OR 1.59).

**Conclusion:** According to this meta-analysis, troponin elevation after elective PCI provides important prognostic information.

## Introduction

Cardiac-specific troponins are useful in establishing diagnosis and predicting prognosis in patients with (suspected) acute coronary syndromes (ACS). Moreover, the sensitivity, specificity and prognostic importance of troponin in ACS are superior compared to creatine kinase (CK) and its muscle-brain isomer (CK-MB) [1-5].
After elective percutaneous coronary intervention (PCI), elevated cardiac enzymes can be observed frequently, even when the procedure is uncomplicated and successful. These elevations of cardiac enzymes have been associated with an increased risk of cardiac events, including death during follow-up, which has been shown clearly for CK and CK-MB in several studies [6-10]. Surprisingly, the association between troponin elevation after elective PCI and cardiac events during follow-up is less clear and conflicting results have been published on this topic [10-36]. However, especially in view of the paucity of outcome, the limitation of many of these studies is the sample size. Furthermore, because of the varying results of the previously performed studies, the results of a single study have to be interpreted with caution as well.
To provide a better overall assessment of the prevalence and prognostic value of cardiac troponin elevation (I and T) after elective PCI in a large cohort, the present meta-analysis was performed.

## Methods

We attempted to obtain results from all published studies on the association between troponin elevation after PCI and cardiac events and/or death in follow-up. Both handsearching of the major general and cardiological journals and electronic searching was performed. The literature was scanned by formal search of electronic databases (MEDLINE, PubMed) using the keywords, “troponin”, “PCI”, “PTCA” and “follow-up”. Furthermore, we reviewed cited references of retrieved articles to identify all possibly relevant studies.
We restricted our review to clinical trials and cohort studies with published data on events in follow-up. Studies that included patients with ST-elevation myocardial infarction as well as studies with severe restrictions for inclusion or exclusion of patients and studies published in a language other than English were excluded. The longest reported follow-up period was used. Furthermore, when more cut-off

values of troponin were used, the lowest available cut-off value was used. In studies reporting subgroups with elevated and non-elevated preprocedural troponin levels, only the subgroup with non-elevated troponin before PCI was included in our meta-analysis, as we were interested in data on elective PCI.

Our primary efficacy of interest was the association between postprocedural troponin elevation and mortality during follow-up. Secondary, the association between troponin elevation and the occurrence of death or myocardial infarction (MI) during the follow-up period was investigated.

Twenty-seven studies were identified initially, including also several studies with unavailable or inappropriate follow-up data. The primary endpoint in our meta-analysis was not specifically reported in 4 studies [20,22,30,31]. In one older study with a very small sample size of 23 patients, an unusually high cut-off value for troponin T was used, and therefore this study was excluded [32]. Another small study on 83 patients had a poor methodology and a high percentage (23%) of patients lost to follow-up [33]. One previously performed meta-analysis was not useful, because of the use of study reports that were available as abstracts only [11]. After excluding these 7 studies, a total of 20 studies were finally suitable for our meta-analysis.

Quantitative variables were expressed as percentages. Differences in outcome between patients with and without increased troponin were reported as odds ratio with 95% confidence intervals, by using the Mantel and Haenszel test. The freely available interactive statistic pages on http://statpages.org were used. A probability value of $p < 0.05$ was considered significant.

**Results**

Twenty studies were included in our analysis [10,12-19,21,23-29,34-36], concerning 17 prospectively and 3 retrospectively performed studies. These studies were published between 1998 and 2007. The number of patients included in the studies varied between 44 and 3494, with a total number of 15,581.

Glycoprotein IIb/IIIa receptor blockers were used in 39.8% of patients, a stent was placed in 80.6%, multivessel PCI was performed in 19.7% and postprocedural troponin was elevated in 32.9% of cases. Troponin I was measured in 14 studies, whereas 6 studies used troponin T; multiple cut-off values were used for both troponins. Baseline characteristics of all studies are summarised in table 1.

**Table 1.** Characteristics of the study populations.

| Author | Year of publi-cation | Study design | Pts. (n) | DM (%) | Renal failure (%) | Gp IIbIIIa use (%) | Stent (%) | Multivessel PCI (%) | Troponin cut-off (ng/ml) | Increased troponin (%) | Increased CK-MB (%) | Primary endpoint reported | Second. endpoint reported |
|---|---|---|---|---|---|---|---|---|---|---|---|---|---|
| *Troponin I* | | | | | | | | | | | | | |
| Attali et al. (29) | 1998 | Retro./cohort | 44 | 6 (14) | - | 0 | 0 | - | 0.35 | 18 (41) | 4 (9) | √ | - |
| Bertinchant et al. (19) | 1999 | Prosp./cohort | 79 | 18 (23) | - | 0 | 46 (58) | 8 (10) | 0.1 | 18 (23) | 12 (11) | √ | √ |
| Fuchs et al (15) | 2000 | Retro./cohort | 1129 | 323 (29) | - | 59 (5) | 822 (73) | - | 0.15 | 345 (31) | 257 (23) | √ | √ |
| Cantor et al. (18) | 2002 | Prosp./ trial | 481 | 85 (18) | - | 103 (21) | 396 (82) | 62 (13) | 1.5 | 230 (48) | 137 (29) | √ | √ |
| Gruberg et al. (21) | 2002 | Retro./cohort | 116 | 56 (48) | 116 (100) | < 3 | 61 (53) | - | 0.15 | 50 (43) | 33 (28) | √ | √ |
| Saadeddin et al. (24) | 2002 | Prosp./cohort | 96 | 55 (57) | - | 0 | 69 (72) | - | 2.0 | 26 (27) | 6 (6) | √ | √ |
| Nallamothu et al. (17) | 2003 | Prosp./cohort | 1157 | 301 (26) | 82 (7) | 868 (75) | 900 (78) | 385 (33) | 2.0 | 336 (29) | - | √ | - |
| Ricciardi et al. (13) | 2003 | Prosp./cohort | 263 | 66 (25) | - | 70 (27) | 193 (73) | 34 (13) | 2.3 | 36 (14) | 34 (13) | √ | √ |
| Kini et al. (16) | 2004 | Prosp./cohort | 2873 | 1178 (41) | - | 2360 (82) | 2501 (87) | 337 (12) | 2.0 | 1121 (39) | 468 (16) | √ | - |
| Natarajan et al. (28) | 2004 | Prosp./cohort | 1128 | 224 (20) | - | 203 (18) | 934 (83) | 153 (14) | 0.1 | 189 (17) | 0 | √ | - |
| Ramirez et al. (23) | 2004 | Prosp./cohort | 147 | 44 (30) | - | 33 (22) | 147 (100) | - | 0.5 | 24 (16) | 23 (16) | √ | √ |
| Cavallini et al. (10) | 2005 | Prosp./cohort | 3494 | 674 (19) | 147 (4) | 706 (20) | 2726 (78) | 1030 (29) | 0.15 | 1544 (44) | 559 (16) | √ | - |
| Okmen et al. (26) | 2006 | Prosp./cohort | 100 | 11 (11) | - | 42 (42) | 85 (85) | 5 (5) | 0.2 | 34 (34) | 6 (6) | √ | √ |
| Izgi et al. (36) | 2006 | Prosp./cohort | 100 | 15 (15) | 0 | 6 (6) | 92 (92) | 10 (10) | 0.08 | 27 (27) | - | √ | √ |
| *Troponin T* | | | | | | | | | | | | | |
| Shyu et al. (25) | 1998 | Prosp./cohort | 120 | 39 (33) | - | 0 | 61 (51) | 28 (23) | 0.1 | 25 (21) | 8 (7) | √ | √ |
| Herrmann et al. (12) | 2002 | Prosp./cohort | 269 | 52 (19) | - | 16 (6) | 269 (100) | 0 | 0.1 | 44 (16) | 44 (16) | √ | √ |
| Kizer et al. (14) | 2003 | Prosp./cohort | 125 | 30 (23) | - | 0 | 9 (7) | 25 (20) | 0.1 | 23 (18) | - | √ | √ |
| Miller et al. (27) | 2006 | Prosp./cohort | 1198 | 297 (25) | - | 730 (61) | 1057 (88) | - | 0.03 | 507 (42) | 417 (21) | √ | √ |
| Prasad et al. (34) | 2006 | Prosp./cohort | 1949 | 532 (27) | 41 (2) | 948 (49) | 1691 (87) | 305 (16) | 0.03 | 383 (20) | 0 | √ | √ |
| Nienhuis et al. (35) | 2006 | Prosp./cohort | 713 | 127 (18) | - | 54 (8) | 501 (70) | 146 (20) | 0.05 | 150 (21) | 66 (9) | √ | √ |
| Total (%) | | | 15581 | 4133 (26.5) | | 6200 (39.8) | 12560 (80.6) | 2528 (19.7) | | 5130 (32.9) | 2074 (14.6) | | |

In the individual studies, several predictors of postprocedural troponin elevation were identified. The most reported predictors were older age, poor LV function (EF <30%), unstable angina, ACC/AHA lesion type B and C, thrombus formation, balloon inflation time, stent implantation, atheroablative devices, abrupt vessel closure, no reflow, dissection and side branch occlusion.

The follow-up period varied between 3 and 67 months (mean 16.3), the average percentage of patients lost to follow-up was 2%. The primary endpoint mortality was reported in all 20 included studies (table 2).

**Table 2.** Outcome according to postprocedural troponin.

| Author | Postprocedural troponin n (%) | | Follow-up | | Mortality n (%) | | | Mortality and/or MI n (%) | | |
|---|---|---|---|---|---|---|---|---|---|---|
| | Troponin + | Troponin - | months | % lost | Troponin + | Troponin - | P | Troponin + | Troponin - | P |
| *Troponin I* | | | | | | | | | | |
| Attali | 18 (41) | 26 (59) | 45 | 2 | 0 | 0 | - | - | - | - |
| Bertinchant | 18 (23) | 61 (77) | 19 | 25 | 0 | 0 | - | 0 | 1 (1.6) | - |
| Fuchs | 345 (31) | 784 (69) | 8 | 12 | 8 (2) | 19 (2) | 0.74 | 9 (3) | 21 (3) | - |
| Cantor | 230 (48) | 251 (52) | 3 | 0 | 4 (1.8) | 1 (0.4) | 0.4 | 24 (10.6) | 11 (4.2) | 0.005 |
| Gruberg | 50 (43) | 66 (57) | 12 | 0 | 14 (28.0) | 7 (9.9) | 0.002 | 17 (33.3) | 9 (13.9) | 0.002 |
| Saadeddin | 26 (27) | 70 (73) | 24 | 0 | 1 (4) | 0 | - | 1 (4) | 0 | - |
| Nallamothu | 336 (29) | 821 (71) | 11 | 0 | 30 (8.9) | 61 (7.4) | - | - | - | - |
| Ricciardi | 36 (13.6) | 227 (86.3) | 12 | 3 | 3 (8) | 16 (7) | - | 5 (14) | 16 (7) | - |
| Kini | 1121 (39) | 1752 (61) | 12 | 0 | 23 (2.0) | 34 (1.9) | 0.58 | - | - | - |
| Natarajan | 189 (17) | 939 (83) | 12 | 0 | 4 (2.1) | 9 (1.0) | - | - | - | - |
| Ramirez | 24 (16) | 123 (84) | 10 | 0 | 1 (4.2) | 0 | - | 2 (8.3) | 0 | - |
| Cavallini | 1544 (44) | 1950 (56) | 24 | 0 | 75 (4.9) | 78 (4.0) | 0.2 | - | - | - |
| Okmen | 34 (34) | 66 (66) | 21 | 0 | 1 (3) | 2 (3) | - | 2 (6) | 3 (4.5) | - |
| Izgi | 27 (27) | 73 (73) | 12 | 0 | 0 | 1 (1) | - | 0 | 1 (1) | - |
| *Troponin T* | | | | | | | | | | |
| Shyu | 25 (21) | 95 (79) | 7 | 0 | 1 (4) | 4 (4) | - | 1 (4) | 4 (4) | - |
| Herrmann | 44 (16) | 225 (84) | 6 | 3 | 4 (9.1) | 2 (0.9) | 0.001 | 5 (11) | 3 (1) | - |
| Kizer | 23 (18) | 102 (82) | 67 | 1 | 3 (13.0) | 11 (10.8) | - | 5 (22) | 16 (16) | - |
| Miller | 507 (42) | 691 (58) | 12 | 10 | 12 (2.4) | 9 (1.3) | 0.52 | 24 (4.7) | 20 (2.9) | 0.16 |
| Prasad | 383 (20) | 1566 (80) | 26 | 0 | 40 (10.4) | 80 (5.1) | <0.001 | 54 (14.1) | 143 (9.1) | 0.004 |
| Nienhuis | 150 (21) | 563 (79) | 11 | 0 | 0 | 9 (1.6) | 0.12 | 6 (4) | 12 (2.1) | 0.20 |
| Total (%) | 5130 (32.9) | 10451 (67.1) | Mean 16.3 | 2 | 224 (4.4) | 343 (3.3) | 0.001 | 155 (8.1) | 260 (5.2) | <0.001 |

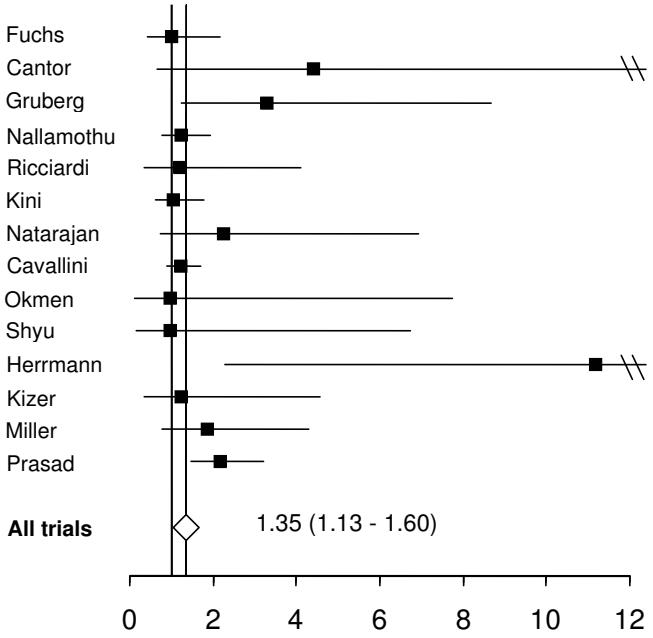


**Figure 1**. Odds ratio (95% CI) for death in pts with increased troponin.

Average mortality was low (3.6%), but significantly higher in patients with troponin elevation after the PCI (4.4% vs 3.3%, p=0.001). The overall odds ratio for mortality according to postprocedural troponin elevation was 1.35 (95% CI 1.13-1.60), as shown in figure 1.

The combined endpoint of mortality or MI during follow-up was reported in 15 studies. This combined endpoint was documented in 6.0% of patients and significantly more often in patients with postprocedural troponin elevation (8.1% vs 5.2%, $p < 0.001$). The odds ratio for the combined endpoint mortality or MI according to postprocedural troponin elevation was 1.59 (95% CI 1.29-1.95), as shown in figure 2.

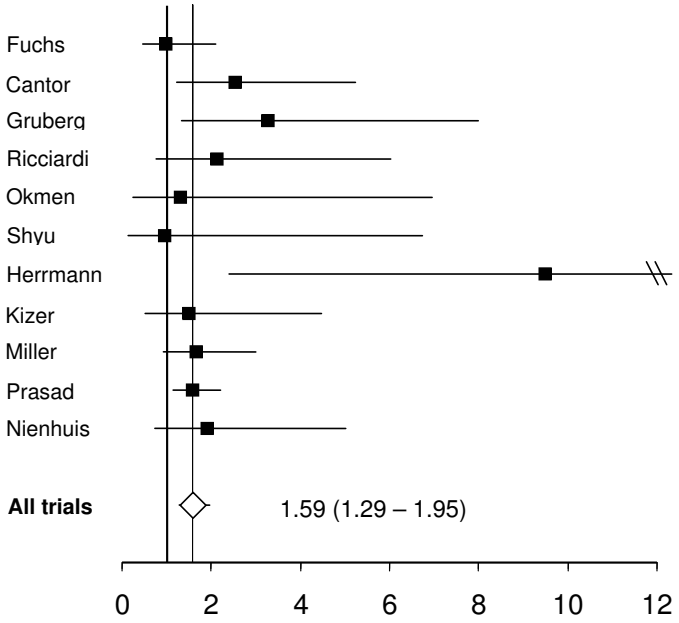


**Figure 2.** Odds ratio (95% CI) for death and/or MI in pts with increased troponin.

## Discussion

The present meta-analysis shows a significant association between troponin elevation after elective PCI and mortality during follow-up. Furthermore, the combined endpoint of mortality or MI in follow-up was also associated with postprocedural troponin elevation.

*Included and other studies*

Previously, one meta-analysis was already performed on this topic, showing an association between troponin elevation and the occurrence of death and MI in follow-up [11]. However, that analysis included many studies that were published as abstracts only. Furthermore, baseline characteristics of the included patients were not reported and a large proportion of that meta-analysis data originated from 1 study. Moreover, the total number of included patients was only 2605, and more recent studies were not included. Cavallini et al showed in a large study on 3494 patients a linear association between 2 years mortality and CK-MB elevation, but not for troponin after PCI [10]. In that study however, most patients

had an acute coronary syndrome. In these patients, elevation of troponin before PCI may have more prognostic importance than post procedural troponin elevations [27]. Remarkably, in studies with a large sample size, the association between troponin and cardiac events during follow-up was less clear than in studies with a small sample size [12,18,20,21,23-25]. This may be due to publication bias, as small studies with negative findings were possibly not published [37]. Specifically, 4 studies found an association between troponin and death and/or MI in follow-up [18,20,21,34], including a retrospective study of patients with chronic renal failure, but not on dialysis [21]. The results of this latter study have to be interpreted with caution, in view of the results of another recently published meta-analysis, showing a strong relation of asymptomatic troponin elevation and prognosis in patients on dialysis [38]. Two included studies investigated the clinical significance of troponin elevation in patients without concomitant CK-MB elevation [28,34]. Although in one study isolated troponin elevations did not predict cardiac events after hospital discharge, in the other study, with a larger patient cohort, elevations were strongly associated with long-term mortality.

*Mechanisms*

There may be several causes for the adverse prognosis of patients with troponin rise after elective PCI. Multiple patient-related factors, including multivessel coronary artery disease, older age, interventions of de-novo lesions, sapheneous vein graft interventions and complex lesions have been related with troponin release after PCI, as well as procedure-related factors such as the no-reflow phenomenon, distal embolisation and side branch occlusion [39]. Studies with magnetic resonance imaging showed that even small increases of CK-MB or troponin are associated with new irreversible myocardial injury [40,41]. Another possible explanation for the worse prognosis of patients with troponin elevation is an increased inflammatory state [42].

The results of the studies performed with post-PCI CK (-MB) elevation were less varying than those with troponin, but most studies on CK (-MB) were performed in a larger sample size [6-10]. However, our meta-analysis showed clearly a significant association between troponin elevation and prognosis. Furthermore, as spontaneous elevation of troponin in patients with ACS is superior to CK (-MB) in predicting (future) cardiac events [1-5] and the adverse consequences of myocardial damage caused by PCI may be similar to spontaneous damage [8],

troponin might be superior to CK (-MB) after PCI in predicting cardiac events as well, although this has been debated [27].

*Limitations*

Several limitations of our review should be noted. First, although there are differences between the types of troponin in e.g. sensitivity and specificity, we included studies on both troponin I and troponin T. Since there is no standard troponin I assay, we could not compare threshold values across studies. Furthermore, although there is a standard troponin T assay (Roche diagnostics), three different cut-off values were used. The total cohort represents a heterogenous mixture of patients undergoing elective PCI, for example balloon/stent implantation and single/multivessel PCI, and most of the included studies reported no detailed analyses of the subgroups. Especially PCI of saphenous vein bypass grafts, which has been shown to be strongly associated with more adverse in-hospital events and lower event-free survival compared to PCI of native arteries [43,44], was unfortunately not specified in most included studies. Therefore, we could not report prognostic value of troponin in subgroups. However, although this heterogenity could have influenced our results somehow, our principal conclusion presumably would be unaffected. Furthermore, as most studies did not report the number of patients with specific causes of postprocedural troponin elevation, a meta-analysis of these causes was not possible. Other potential reasons for troponin elevation, e.g. pulmonary embolism, renal failure were not, or only limited reported in the individual studies. The follow-up periods in the included studies varied, and if prognostic value of troponin is time-dependent, this could have influenced the findings. Another limitation of our study is the chosen endpoint, which did not include target vessel revascularization during follow-up. However, as this latter endpoint was reported in only a few studies and may be considered as weak, for this meta-analysis only the hard endpoints death or MI were chosen. Because not all included studies focused on the same endpoint, from some studies we only used a part of the reported results. Finally, potential under-reporting of negative studies may have increased the strength of association between troponin and outcome.

*Conclusion and implications*

The use of troponin after elective PCI is not recommended by the recently revised European guidelines [45], based on only 3 studies and the previously performed meta-analysis with the already mentioned important limitations [11]. Routine

measurement of troponin and/or CK-MB seems to be reasonable according to the recently revised ACC/AHA guidelines, whereas determining these biomarkers is advised for patients with signs or symptoms suggestive of MI or angiographic evidence of complications after PCI [46]. According to the results of our meta-analysis, cardiac troponins offer important prognostic information after elective PCI. The remaining questions are whether troponin has to be used in daily practise next to, or instead of CK(-MB) and whether determining troponin can be cost-effective. Furthermore, still have to be determined whether more intensive monitoring and treatment of patients with increased troponin after elective PCI will reduce future cardiac events.

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# Part II

# Myocardial injury around primary PCI

# Chapter 6

# Predictors of elevated cardiac troponin T on admission in ST-segment elevation myocardial infarction

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**ABSTRACT**

**Background:** In patients with ST-segment elevation acute myocardial infarction (STEMI), elevated cardiac troponin T (cTnT) on admission is associated with poorer outcomes despite early reperfusion. Presentation delay is thought to the be most important factor for the elevation of cTnT on admission. We evaluated presentation delay and other potential predictors of elevated cTnT on admission in patients treated with primary percutaneous coronary interventions (PCI) for STEMI.

**Methods:** CTnT was measured upon arrival in the PCI centre in 444 patients with acute STEMI. An elevated cTnT was defined as > 0.05 µg/L.

**Results:** Mean age was 61.7 year and the patients were admitted after a median of 155 minutes after symptom onset. Almost 50% had an elevated cTnT on admission. Patients with a positive cTnT on admission had less often successful primary PCI (87% vs. 93%, p=0.048) and significantly higher rates of one year mortality (4.9% vs. 1.3%, p=0.031). There was a significant association between presentation delay and the prevalence of elevated admission cTnT, but even patients with early presentation (<120 minutes after symptom onset) still had a high prevalence of elevated cTnT (33%). After multivariate analysis, apart from presentation delay, anterior myocardial infarction (MI) location and higher age were independent predictors of elevated cTnT on admission.

**Conclusion:** In patients with STEMI, the prevalence of elevated cTnT on admission is high, even in patients with early presentation. Independent predictors of elevated cTnT on admission are presentation delay, increasing age and anterior MI infarction location.

## Introduction

Several studies have demonstrated that an elevated cardiac troponin T (cTnT) on admission in patients with ST-segment elevation myocardial infarction (STEMI), predicts short- and long term mortality and failure of thrombolytic therapy or primary percutaneous coronary interventions (PCI) [1-5]. Giannitsis et al [6] found that elevated cTnT on admission in STEMI predicts lower rates of post procedural Thrombolysis in Myocardial Infarction (TIMI) grade 3 flow, more severely compromised myocardial perfusion despite normal epicardial flow and higher rates of all cause and cardiac mortality. They also concluded that cTnT-positive patients might require more aggressive adjunctive therapy when treated with primary PCI. Although cTnT may be elevated even within 2 hours after symptom onset [3,6], it is generally believed that cTnT elevations are mostly seen at a minimum of 3-4 hours after the onset of chest pain [7].
Previous reports were hampered by relative small sample sizes and predictors of elevated cTnT on admission are not yet clear. The present study was designed to identify the independent predictors of elevated cTnT on admission in a large population of STEMI patients treated with primary PCI and to study the mechanism of cTnT elevation early after symptom onset.

## Patients and Methods

From June 2001 to November 2002, 507 consecutive patients were enrolled in the On-TIME trial. Patients with STEMI, who were transferred to a PCI centre, were randomised to early (pre-hospital) or late (in the catheterization laboratory) initiation of tirofiban. Inclusion and exclusion criteria have been described previously [8]. In brief: patients with chest pain of > 30 minutes' duration and ECG changes with ST segment elevation > 2 mm in the precordial leads or >1 mm in the limb leads in at least 2 contiguous leads were included in the study. The ability to perform PCI within 6 hours after symptom onset was also an enrolment criterion. The exclusion criteria were age over 80 years, women less than 50 years of age, patients who were treated with thrombolytic therapy in the previous 24 hours, patients on warfarin or acenocoumarol within the last 7 days and patients with a contraindication to glycoprotein IIb/IIIa blockade. Patients with severe heart failure or cardiogenic shock and patients who were on hemodialysis were also excluded.

Each institution's Review Board or Ethical Committee approved this study. All patients gave written informed consent. The study population consisted of 444 patients (88%), by whom cTnT was measured on admission. Patients were stratified into cTnT-positive and cTnT-negative. Baseline characteristics, angiographic parameters and clinical outcome were compared between the cTnT-positive and cTnT-negative patients. Presentation delay was defined as the time from symptom onset to infarct diagnosis (first ECG). Ischemic time was defined as time from symptom onset to first balloon inflation.

*Serum marker analyses*

CTnT levels were measured by using a point-of-care system (Cardiac reader, Roche Diagnostics, Almere, Netherlands). CTnT > 0.05 µg/L was considered as positive. Creatine kinase (CK), creatine kinase MB (CK-MB) activity and cumulative Lactate Dehydrogenase (LDHQ48) concentrations were analysed with the Elecsys 2010 system (Roche Diagnostics). Glucose was measured by a hexokinase method using a Modular PPE module device (Roche Analytics, Almere, Netherlands). High sensitivity C-reactive protein (HsCRP) was measured by immunochemical analyses of HsCRP (Modular, Roche, Almere, Netherlands) and the White blood cell count (WBC) is determined on the Sysmex XE 2100 (Goffin Meyvis, Etten-Leur, Netherlands).

To evaluate the relation between symptom onset to admission time and elevating cTnT, we stratified the patients according to presentation delay in an early group who presented within 120 min after the onset of symptoms, an intermediate group, who presented between 120 and 180 minutes and a late group who presented later than 180 minutes.

*Angiographic data analysis*

All angiograms were analyzed by an independent core lab (Diagram B.V., Zwolle, The Netherlands) who were blinded to all data. Apart from the coronary angiogram; TIMI flow grades and myocardial blush grade (MBG) were assessed after the angioplasty procedure, as previously described [9,10]. Residual stenosis was assessed visually. Procedural success was defined as postprocedural TIMI 3 flow of the infarct related vessel (IRV) and residual stenosis less than 50%. Left ventricle ejection fraction (LVEF) was assessed angiographically.

*ST-segment resolution*

For assessment of ST-segment resolution, serial 12-lead ECG recordings just before PCI and immediately after return to the coronary care unit were analysed by the same core lab blinded to the clinical data. ECG's with bundle-branch block, pacemaker rhythm, or incomplete or poorly interpretable ECG recordings were not included in this analysis. The ST segment in the lead showing maximal deviation was measured 60 ms after the J point. The resolution of the ST segment was calculated in relative reductions from baseline expressed as percentage.

*Follow-up*

Records of included patients who visited our outpatient clinic were reviewed. For all other patients, information was obtained from the patient's general physician or by direct telephone interview with the patient. For patients who died during follow-up, hospital records and necropsy data were reviewed. Patients were followed up prospectively for one year by use of hospital records, questionnaire, and telephone contact.

*Statistical analysis*

Statistical analysis was performed with the Statistical Package for the Social Sciences (SPSS Inc., Chicago, IL, USA) version 12.0.1. Continuous data were expressed as mean ± standard deviation of mean or median and 25-75 percentile and categorical data as percentage, unless otherwise denoted. The analysis of variance and the chi-square test were appropriately used for continuous and categorical variables respectively. A multivariate logistic regression analysis was performed to identify independent predictors of high troponin level at admission. Significant variables analyzed are reported with their respective odd ratios and 95% confidence intervals. For all analyses, statistical significance was assumed when the two tailed probability value was $<0.05$.

**Results**

*Baseline*

CTnT on admission was measured in 444 patients. Mean age of these patients was 61.7 years and they were admitted after a median of 155 minutes after symptom onset. Almost 50% of the patients had an elevated cTnT on admission.

Clinical characteristics of the study group stratified by admission cTnT are displayed in table 1. Patients with elevated cTnT on admission were significantly older, more often female, had more often a heart rate >100 bpm or an anterior myocardial infarct location. Presentation delay (median 106 vs. 80 min.) was longer and Killip class > 1 was significantly more often present in the cTnT positive patients.

**Table 1.** General Characteristics.

| Variable | cTnT-positive (n=208, 47%) | cTnT-negative (n=236, 53%) | p-value |
|---|---|---|---|
| Age (years ± sd) | 64 ± 11 | 60 ± 10 | < 0.001 |
| Female gender n, (%) | 49 (24) | 37 (16) | 0.04 |
| Diabetes mellitus, n (%) | 26 (13) | 18 (8) | 0.09 |
| Hypertension, n (%) | 60 (29) | 64 (27) | 0.7 |
| Hyperlipidemia, n (%) | 42 (20) | 61 (26) | 0.2 |
| Smoking, n (%) | 128 (62) | 150 (65) | 0.5 |
| Heart rate >100 bpm, n (%) | 26 (13) | 8 (4) | < 0.001 |
| Previous MI, n (%) | 14 (7) | 25 (11) | 0.2 |
| Previous PCI, n (%) | 7 (3) | 17 (7) | 0.08 |
| Previous CABG, n (%) | 3 (1) | 8 (3) | 0.2 |
| Anterior infarction, n (%) | 115 (57) | 75 (34) | < 0.001 |
| Presentation delay (min) | 106 (63-182) | 80 (50-128) | < 0.001 |
| Killip class >1, n (%) | 42 (22) | 23 (11) | 0.003 |
| Glucose (± SD) | 9.92 (3.77) | 9.46 (2.58) | 0.1 |
| CK on admission U/L | 190 (125-348) | 98 (70-148) | < 0.001 |
| CK peak U/L, | 1879 (804-3889) | 1489 (661-3027) | 0.007 |
| CK-MB on admission U/L | 21 (14-38) | 12 (9-15) | < 0.001 |
| CK-MB peak U/L | 229 (89-425) | 189 (76-307) | < 0.001 |
| $LDHQ_{48}$ | 1419 (439-2838) | 1093 (441-2119) | 0.10 |
| WBC $10^9$/L | 11.8 ± 3.5 | 11.9 ± 3.6 | 0.8 |
| HsCRP, mg/L | 3.1 (1.4-6.0) | 2.3 (1.3-4.5) | 0.02 |
| Early tirofiban initiation, n (%) | 112 (54) | 106 (45) | 0.06 |
| Cum. ST-elevation (mm) (± SD) | 11 ± 8 | 9.5 ± 7 | 0.07 |
| ST resolution, % (± SD) | 73 ± 29 | 74 ± 39 | 0.9 |

Values given as means with SD in parentheses or as absolute numbers with relative frequencies. Presentation delay, CK, CK-MB, $LDH_{Q48}$ and HsCRP are given as median and 25-75 percentile. $LDHQ_{48}$ = Enzymatic infarct size (area under the lactate dehydrogenase release over 48h curve). HsCRP = high-sensitive C-reactive protein.

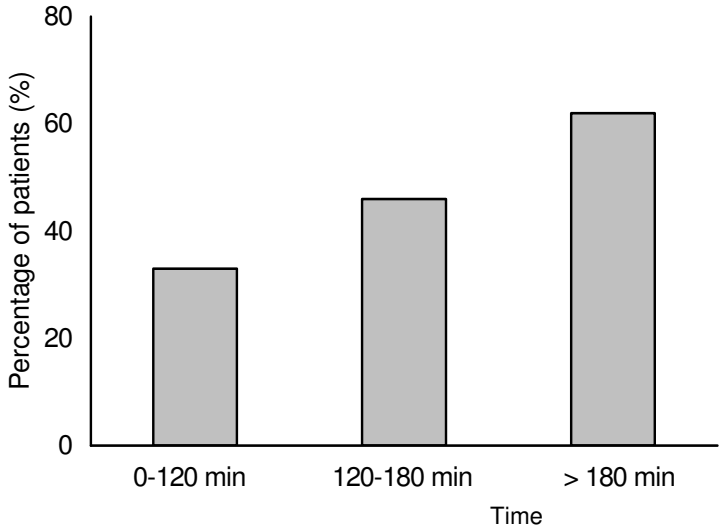


**Figure 1.** Prevalence of elevated cTnT on admission according to time from symptom onset to admission.

Admission CK and CK-MB were significantly higher in the cTnT positive patients. WBC was comparable in both groups but HsCRP was significantly higher in the cTnT positive patients. Prevalence of elevated admission cTnT was 33% in the early, 46% in the intermediate and 62% in the group with long presentation delay (figure 1). Prevalence of increased cTnT was 54% in the early tirofiban group, compared to 46% in the late tirofiban group (p =0.06).

*Angiographic findings*

Multivessel disease and thrombus load were comparable in cTnT positive- and cTnT negative patients (56% vs. 54% and 31% vs. 27%, respectively) (table 2). Pre PCI TIMI 3 and TIMI 2,3 were significantly higher in the cTnT positive patients (21% vs. 13%, p =0.03 and 45% vs. 32%, p =0.008, respectively). Both post PCI TIMI 3 flow and MBG 3 were significantly lower in the cTnT positive patients (87% vs. 93%, p =0.048 and 42% vs. 63%, p <0.001, respectively). LVEF was significantly lower in the cTnT positive patients.

**Table 2.** Angiograpic parameters pre- and post PCI.

| Variable | cTnT positive (n=208, 47%) | cTnT negative (n=236, 53%) | p-value |
|---|---|---|---|
| *Pre-PCI* | | | |
| Multivessel Disease, n (%) | 115 (56) | 122 (54) | 0.7 |
| TIMI 3 | 43 (21) | 29 (13) | 0.03 |
| TIMI 2,3 | 92 (45) | 72 (32) | 0.008 |
| Thrombus | 63 (31) | 60 (27) | 0.4 |
| *Post-PCI* | | | |
| TIMI 3 | 161 (87) | 197 (93) | 0.048 |
| MBG 3 | 78 (42) | 132 (63) | <0.001 |
| Coronary stenting, n (%) | 127 (69) | 153 (74) | 0.3 |
| LVEF | 42 ± 12 | 47 ± 9 | <0.001 |

TIMI = thrombolysis in myocardial infarction**,** MBG = myocardial blush grade

*Infarct size and outcome*

$LDHQ_{48}$ and cumulative ST- segment elevation tended to be higher in the cTnT positive patients. No significant difference was found in ST segment resolution between cTnT positive and cTnT negative patients (table 1).

At 30 days, cardiac and all-cause mortality tended to be higher in the cTnT positive patients. At one year, cardiac death (3.4% vs. 0.4%, p =0.03) and all-cause mortality (4.9% vs. 1.3%, p =0.03) were significantly higher in cTnT positive patients. Rates of combined reinfarction and/or death were not statistically different in both groups (figure 2).

*Multivariate analysis*

To assess the independent predictors of an elevated cTnT on admission, we performed a multivariate analysis and included age, gender, infarct location, Killip class, diabetes, previous PCI, heart rate>100 bpm, Hs CRP and presentation delay. Age (years), Hs CRP (mg/ml) and presentation delay (minutes) were included as continuous variables. Multivariate analysis revealed that age, (OR 1.03; 95%CI: 1.01-1.06, p =0.01), anterior myocardial infarction (OR 2.98; 95%CI: 1.78-4.99, p <0.001) and presentation delay per 30 minutes (OR 1.23; 95%CI: 1.10-1.34, p <0.001) were independent predictors of an elevated cTnT on admission (table 3).

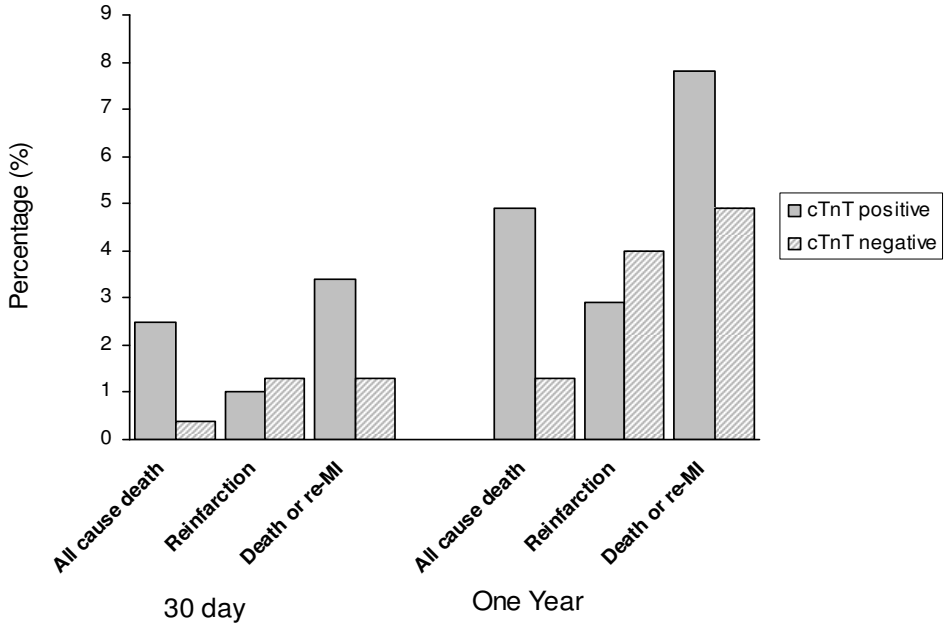


**Figure 2.** Short- and long-term outcomes. At 30 days rates of cardiac death and all causes of mortality were not significantly different between both groups. However, at one year rates of cardiac death and all causes of mortality were significantly higher in the cTnT positive patients.

**Table 3.** Predictors of troponin T elevation, multivariate analysis.

| Variable | OR | 95% CI | P |
|---|---|---|---|
| Age (per year) | 1.03 | 1.01-1.06 | 0.01 |
| Anterior infarction | 2.98 | 1.78-4.99 | < 0.001 |
| Presentation Delay (per 30 min.) | 1.23 | 1.10-1.34 | < 0.001 |
| Diabetes | 0.64 | 0.25-1.06 | 0.3 |
| Previous PCI | 0.31 | 0.09-1.05 | 0.06 |
| Female gender | 1.41 | 0.72-2.76 | 0.3 |
| Heart rate >100 bpm | 4.74 | 0.81-27.6 | 0.08 |
| Killip class >1 | 1.86 | 0.72-4.76 | 0.2 |
| Hs CRP (per mg/L) | 1.01 | 0.99-1.40 | 0.2 |

Hs CRP = high-sensitive C-reactive protein

## Discussion

This study demonstrates that apart from presentation delay, anterior myocardial infarct location and higher age are also independent predictors of elevated cardiac troponin T on admission. Elevated cTnT on admission is associated with worse angiographic and clinical outcome, despite primary PCI and treatment with tirofiban.

*Predictors of elevated cTnT on admission*

Our data show that in patients with STEMI, cTnT identifies a high risk group, characterized by Killip class > 1, elderly and patients with anterior myocardial infarct location. A previous study [7] emphasized that troponin T elevations are only seen at a minimum 3-4 hours after the onset of symptoms. Other studies, however, reported an elevated TnT on admission even within 2 hours after symptom onset [3,6].

We consistently found that admission delay was associated with elevated troponin on admission [6]. Nevertheless, almost 50% of the patients had an elevated cTnT on admission, whereas even patients with short presentation delay (<120 minutes after symptom onset) had a relatively high prevalence of elevated cTnT (33%). Why patients with short symptom duration would have an elevated cTnT on admission is not yet clear. In these patients the onset of symptom may have gone undetected and thus the true onset of the infarction could have begun much earlier. They could have had a previous silent event that caused cTnT release [3]. Previous study reported that acute coronary occlusion in STEMI, is often the final stage in a series of successive events that occurred in the preceding days or weeks [11]. Other possible explanation of elevated cTnT short after symptom onset is a large area at risk, cTnT positive patients had higher levels of peak CK-MB and lower LVEF (table 1, table 2). Furthermore, the absence of collaterals may also explain the elevated troponin on admission. Matetzky et al found that patients with elevated troponin have less frequently collateral blood flow [5]. In addition, in the current study patients with elevated cTnT on admission more often had a Killip class>1 and we previously reported that a Killip class > 1 is associated with worse outcome in STEMI patients [12].

*Prognostic value*

Previous studies have demonstrated that both thrombolysis and primary PCI therapy are less effective in cTnT positive patients [2,4,5,13]. Others have found

that epicardial flow (TIMI flow <3) remained more frequently compromised and myocardial reperfusion (as measured by serum cardiac markers) was more impaired in cTnT-positive than in cTnT-negative patients [6].
Our data confirm that elevated cTnT is associated with impaired myocardial perfusion, as measured by MBG, and lower rates of post-PCI epicardial TIMI 3 flow. Previous studies [14,15] showed that pre-procedural patency (TIMI 2 or 3) is associated with favorable outcome. In our study we found that outcome was worse in cTnT positive patients, although these patients had higher initial patency rate of the infarct related vessel (IRV). This may be caused by early washout of cardiac enzymes in patients who presented with open IRV (table 2). In addition, the higher rates of TIMI 3 flow in cTnT positive patients could also be explained by the higher rates of anterior myocardial infarct location (table 1), since it has been found that patients with an anterior myocardial infarct location more often have a patent IRV than non anterior infarct location [16]. In addition, our study confirms the results of a previous study [17] that found an inverse relation between LVEF and cTnT. Furthermore, our results are consistent with Kurowski et al, who found a poorer outcome in patients with elevated troponin as compared to patients with normal troponin values on admission [18].

*Implication for treatment*
Because elevated cTnT on admission have a worse prognosis, efforts should be made to improve their treatment. Although in a general population with STEMI treated with primary PCI and coronary stenting, glycoprotein IIb/IIIa inhibitors have limited value [19], in patients with elevated cTnT on admission there may be more clear effects.

*Limitations*
This study is a post-hoc, observational analysis and the results were obtained in patients who underwent primary PCI and may not relate to patients treated with thrombolytic therapy. Second, troponin T was measured using a point-of-care reader allowing only identifying patients with troponin levels above 0.05 µg/L. However, by definition, patients with levels above 0.03 µg/L are classified as non-STEMI and increased risk has been reported by the TACTICS TIMI 18 Study Group even at levels close to the lower detection limit [20]. Thus, it is likely that the On-Time study has underestimated the true proportion and risk in this subset. Nevertheless, studies using higher cut-off values found similar results [3,6].

Another limitation is that we measured CK-MB activity and not CK-MB mass, however, CK-MB mass is more sensitive and more specific.

*Conclusion*

This study shows a high prevalence of elevated cardiac troponin T on admission in patients with STEMI treated with primary PCI, even in patients who presented early after symptom onset. Apart from presentation delay, increasing age and anterior infarct location are also independent predictors of elevated cTnT on admission.

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# Chapter 7

# Prognostic importance of creatine kinase and creatine kinase-MB after primary PCI for ST elevation myocardial infarction

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**ABSTRACT**

**Background:** Although the prognostic significance of CK and CK-MB after myocardial infarction has been established after thrombolysis or no reperfusion therapy, there is limited evidence of the prognostic importance after primary percutaneous coronary intervention (PCI).

**Methods:** In this prospective, observational study, individual data from all patients who survived at least 2 days after primary PCI between 1991 and 2004 in our hospital were recorded. The association between enzymatic infarct size (examined by peak CK and peak CK-MB levels, each divided into tertiles) and both LV ejection fraction and one-year mortality was evaluated.

**Results:** In the study group of 4670 patients, mean peak CK was 2327 U/L (SD±2008) and mean peak CK-MB was 244 U/L (SD±208). Both increased CK and CK-MB were associated with a lower LV ejection fraction. A total of 252 patients (5.4%) died between 2 days and one year after admission. Both peak CK and peak CK-MB were higher in those who died. Particularly, patients in the highest tertile of either peak CK or peak CK-MB had increased mortality, whereas the differences between the lower tertiles were not significant. In 2738 patients, after multivariable analysis including LV ejection fraction, the hazard ratio for one-year mortality in patients in the highest CK tertile was 2.28 (95% CI 1.32-3.91) and for CK-MB 1.91 (95% CI 1.11-3.26), compared to those in the other tertiles.

**Conclusion:** According to this large-scale study, peak CK and peak CK-MB are comparable independent predictors of LV-function and one-year mortality in patients after primary PCI.

## Introduction

The adverse prognostic significance of biomarker elevations during myocardial infarction (MI) has been subject for many studies in the past decades. Peak levels of aspartate aminotransferase (ASAT), lactate dehydrogenase (LDH), creatine kinase (CK) and its muscle brain isomer (CK-MB) have been shown to be reliable predictors of infarct size and prognosis in patients suffering MI [1-7]. Furthermore, the cumulative CK and LDH curve areas are also well correlated with infarct size [8,9].

Over the past years, primary percutaneous coronary intervention (PCI) has become the preferred therapy for patients with ST-elevation myocardial infarction (STEMI) [10,11]. However, the above mentioned studies on biomarkers have been performed in patients receiving thrombolytics or no reperfusion therapy at all. Only two large-scale studies have been published in patients undergoing primary PCI for STEMI, one showing that the cumulative extent of LDH is an independent predictor of one-year mortality [12] and the other that peak CK level is associated with increased one-year mortality [13]. The latter study, however, did not assess the potential importance of CK-MB.

To address this issue, we performed a prospective study on patients undergoing primary PCI for STEMI, focusing on both peak CK and CK-MB levels and their potential relation to left ventricular ejection fraction (LVEF) and mortality.

## Methods

*Population*

From January 1991 to December 2004, individual patient data from all patients with admission diagnosis of STEMI admitted for primary PCI at the Isala klinieken (Zwolle, the Netherlands) were prospectively recorded. Patients who died during the first 2 days were not included in this sub-study, because many of these patients died before peak CK was recorded. Furthermore, patients with peak CK values > 10.000 U/L were excluded, as these high elevations of CK were probably at least partly due to rhabdomyolysis. To avoid double inclusion of patients, only the first recorded admission for STEMI during the study period was used. Patients were diagnosed with STEMI if they had chest pain of > 30 minutes' duration and ECG changes with ST segment elevation > 2 mm in at least 2 precordials and > 1 mm in the limb leads. Before the primary PCI procedure, all patients received 500

mg of aspirin and 5000 IU of heparin intravenously. Primary PCI was performed with standard techniques if the coronary anatomy was suitable for angioplasty. PCI success was determined by the classification system of the Thrombolysis in Myocardial Infarction (TIMI) trial, in which a grade 3 blood flow indicates normal flow within the vessel, in combination with a myocardial blush grade 2 and 3 [14]. Additional treatment with GP IIb/IIIa-inhibitors or stents was to the discretion of the treating cardiologist. All patients were treated with optimized drug-therapy including angiotensin-converting enzyme inhibitors, β-blockers, aspirin and lipid-lowering drugs where appropriate.

*Measurements*

Protocol-specified blood sampling for CK and CK-MB levels was performed at baseline and at 8 hours, 16 hours and 24 hours after PCI. Measurement of serum total CK and CK-MB levels was performed according to our local hospital standards, which did not change over the course of the study. LVEF was measured before discharge by radionuclide ventriculography or by echocardiography if the patient had atrial fibrillation. Radionuclide ventriculography was performed by using the multiple gated equilibrium method following the labelling of red blood cells of the patient with 99mTc-pertechnate. A General Electric 300 gamma camera with a low-energy all-purpose parallel-hole collimator was used. Global ejection fraction was calculated by a General Electric Star View computer using the fully automatic PAGE program. In patients with atrial fibrillation, standard 2-dimensional and Doppler imaging was performed and stored in cineloop format by well-trained echocardiographists and reviewed by experienced cardiologists. The LV end-diastolic volume (LVEDV) and end-systolic volume (LVESV) were measured [15] and the LV ejection fraction was calculated as (LVEDV-LVESV)/LVEDV x 100% (Simpson's rule). A low LVEF was defined as an ejection fraction ≤ 30%. Ischemic time was defined as time from symptom onset to first balloon inflation. The definition of multivessel disease was a stenosis in at least one non-culprit coronary artery of more than 50%, as judged by 2 experienced cardiologists or by quantitative coronary analysis.

Follow-up information was obtained from the patient's general physician or by direct telephone interview with the patient or it's relatives. Events were confirmed by reviewing the concerning letter to the general physician or patient's clinical file if necessary, and all cause mortality was reported. Re-MI was defined as anginal complaints with new CK(-MB) elevation and/or new Q-waves on the

electrocardiogram in follow-up. Study approval was obtained from the medical ethic committee of our hospital.

*Statistical Analysis*

Statistical analysis was performed with the Statistical Package for the Social Sciences (SPSS Inc., Chicago, IL, USA) version 12.0.1. Outcomes were examined stratified by peak CK and peak CK-MB levels, divided into three equal tertiles. Univariate differences between groups were analyzed with one-way analysis of variance or by chi square test as appropriate, with Bonferroni correction for multiple comparisons. Cox proportional-hazards regression models were used to estimate the risk of mortality after one year. Separate analyses were performed in patients with known LV ejection fraction, since 41% of these data were missing. Multivariable analyses were performed with the Cox models for all cause mortality and with a logistic regression model to assess risk of low LV ejection fraction. In this analysis, patients in the highest tertile of CK or CK-MB were compared to those in the lower tertiles. Significant variables analysed are reported with their respective hazard ratios (HR) and 95% confidence intervals (CI). For all analyses, statistical significance was assumed when the two-tailed probability value was $< 0.05$.

## Results

*Baseline characteristics*

Of the 4670 included patients, mean age was 60.8 years (SD 11.8) and 1102 patients (24%) were female. Data on peak CK and peak CK-MB were available in all patients. Mean peak CK was 2327 U/L (SD 2008) and mean CK-MB 244 (SD 208). The range in the 3 tertiles was respectively <1080 U/L, 1080-2660 U/L and >2660 U/L for CK, and <120 U/L, 120-281 U/L and >281 U/L for CK-MB. Differences of the baseline characteristics between the tertiles of CK are summarised in table 1 and of CK-MB in table 2. Patients with higher peak CK and peak CK-MB values were more likely to be younger and smoker, but were less likely to have previous history of coronary bypass surgery, PCI or MI. Patients with higher peak CK (-MB) values also had more often anterior infarction, higher Killip class on presentation, TIMI 0 flow pre-PCI and less often TIMI 3 flow post-PCI.

*Outcome*

Data on LVEF were available in 2738 patients (59%). Patients in the medium and highest tertile of CK and CK-MB had significantly lower LVEF and a longer hospital stay compared to patients in the lowest tertile, as shown in table 3 and table 4. Prevalence of a low LVEF in the tertiles of CK and CK MB are shown in figure 1.

**Table 1**. Baseline characteristics according to tertiles of peak CK in 4670 pts who survived at least 2 days after primary PCI for ST-elevation MI.

| Variables | Lowest<br>n = 1554 | Medium<br>n = 1560 | Highest<br>n = 1556 |
|---|---|---|---|
| Age, yr±sd | 62.2±11.5 | 61.6±11.9 | 59.4±12.0 # |
| Female gender | 429 (28%) | 377 (24%) | 296 (19%) ^ |
| *History of* | | | |
| MI | 225 (15%) | 185 (12%) | 154 (10%) # |
| CABG | 62 (4%) | 48 (3%) | 29 (2%) # |
| PCI | 116 (8%) | 104 (7%) | 65 (4%) # |
| Stroke | 57 (4%) | 40 (3%) | 55 (4%) |
| Hypertension | 477 (31%) | 424 (28%) | 431 (28%) |
| Diabetes | 190 (12%) | 138 (9%) * | 167 (11%) |
| Hyperlipidemia | 338 (23%) | 333 (23%) | 287 (20%) |
| Family CVD | 639 (43%) | 648 (43%) | 651 (43%) |
| Smoke | 674 (44%) | 715 (47%) | 849 (56%) # |
| Killip class > 1 | 88 (6%) | 123 (8%) | 217 (14%) # |
| Ischemic time, hr±sd | 4.6±5.7 | 5.0±6.8 | 4.7±4.6 |
| Anterior MI | 668 (44%) | 617 (40%) | 984 (63%) # |
| Multivessel disease | 771 (51%) | 853 (56%) $ | 805 (52%) |
| TIMI 0 flow pre-PCI | 536 (39%) | 1010 (68%) # | 1161 (78%) # |
| Stent implantation | 749 (54%) | 789 (53%) | 907 (60%) ^ |
| TIMI 3 flow post-PCI | 1250 (91%) | 1295 (87%) $ | 1284 (86%) # |

$ p < 0.05; * p < 0.01; ^ p < 0.005; # p < 0.001 compared to lowest tertile
p-values adjusted for multiple comparisons

**Table 2**. Baseline characteristics according to tertiles of peak CK- MB in 4670 pts who survived at least 2 days after primary PCI for ST-elevation MI.

| Variables | Lowest n = 1541 | Medium n = 1554 | Highest n = 1575 |
|---|---|---|---|
| Age, yr±sd | 61.6±11.6 | 61.3±11.9 | 60.4±12.1 $ |
| Female gender | 385 (25%) | 365 (24%) | 352 (22%) |
| History of | | | |
| MI | 236 (15%) | 185 (12%) $ | 143 (9%) # |
| CABG | 61 (4%) | 49 (3%) | 29 (2%) # |
| PCI | 119 (8%) | 101 (7%) | 65 (4%) # |
| Stroke | 56 (4%) | 34 (2%) | 62 (4%) |
| Hypertension | 469 (31%) | 434 (28%) | 429 (28%) |
| Diabetes | 174 (11%) | 163 (11%) | 157 (10%) |
| Hyperlipidemia | 346 (24%) | 332 (23%) | 280 (19%) ^ |
| Family CVD | 633 (43%) | 664 (44%) | 640 (42%) |
| Smoke | 671 (44%) | 729 (48%) | 837 (55%) # |
| Killip class > 1 | 99 (7%) | 121 (8%) | 207 (13%) # |
| Ischemic time, hr±sd | 4.7±6.4 | 4.5±4.2 | 5.1±2.9 |
| Anterior MI | 668 (44%) | 624 (40%) | 976 (62%) # |
| Multivessel disease | 767 (51%) | 840 (55%) | 821 (53%) |
| TIMI 0 flow pre-PCI | 522 (39%) | 983 (66%) # | 1201 (79%) # |
| Stent implantation | 720 (52%) | 790 (53%) | 935 (61%) # |
| TIMI 3 flow post-PCI | 1220 (91%) | 1315 (88%) | 1293 (85%) # |

$ p < 0.05; ^ p < 0.005; # p < 0.001 compared to lowest tertile
p-values adjusted for multiple comparisons

**Table 3**. Prognosis according to tertiles of peak CK in 4670 pts who survived at least 2 days after primary PCI for ST-elevation MI.

| Variables | Lowest n = 1554 | Medium n = 1560 | Highest n = 1556 |
|---|---|---|---|
| Mean LVEF (%) | 50.5±10.9 | 46.8±10.3 # | 38.5±11.1 # |
| Mean hospital stay (days) | 4.7±7.0 | 5.2±5.7 $ | 5.5±6.4 # |
| Outcome after one-year: | | | |
| Death | 57 (4%) | 63 (4%) | 132 (9%) # |
| Death/re-MI | 118 (8%) | 132 (8%) | 195 (13%) # |
| Stroke | 12 (1%) | 18 (1%) | 15 (1%) |
| CABG | 200 (13%) | 219 (14%) | 186 (12%) |
| PCI | 218 (14%) | 248 (16%) | 237 (15%) |
| re-MI | 66 (4%) | 75 (5%) | 82 (5%) |

$ p < 0.05; # p < 0.001 compared to lowest tertile
p-values adjusted for multiple comparisons

**Table 4**. Prognosis according to tertiles of peak CK-MB in 4670 pts who survived at least 2 days after primary PCI for ST-elevation MI.

| Variables | Lowest n = 1541 | Medium n = 1554 | Highest n = 1575 |
|---|---|---|---|
| Mean LVEF (%) | 50.8±10.7 | 46.5±10.4 # | 38.4±11.1 # |
| Mean hospital stay (days) | 4.7±6.6 | 5.5±6.3 ^ | 5.3±6.3 $ |
| Outcome after one-year: | | | |
| Death | 57 (4%) | 58 (4%) | 137 (9%) # |
| Death/re-MI | 114 (7%) | 131 (8%) | 200 (13%) # |
| Stroke | 12 (1%) | 12 (1%) | 21 (1%) |
| CABG | 211 (14%) | 211 (14%) | 183 (12%) |
| PCI | 216 (14%) | 261 (17%) $ | 225 (14%) |
| re-MI | 62 (4%) | 81 (5%) | 80 (5%) |

$ p < 0.05; ^ p < 0.005; # p < 0.001 compared to lowest tertile
p-values adjusted for multiple comparisons

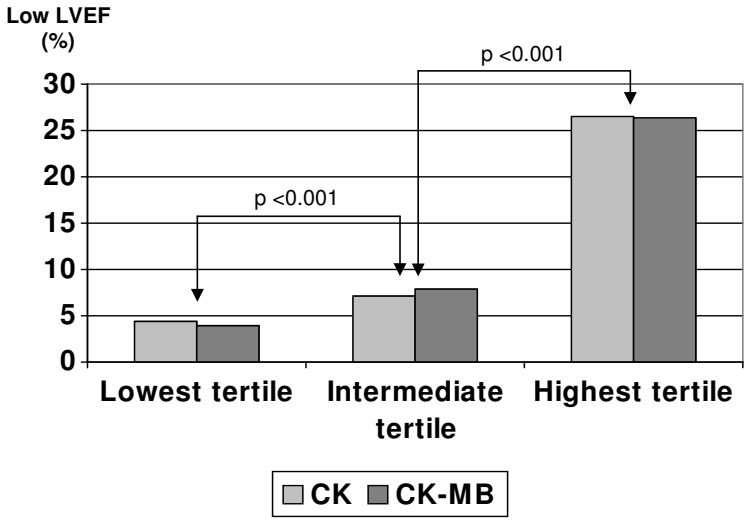


**Figure 1.** Prevalence of a low LVEF (< 30%) in tertiles of peak CK and peak CK-MB.

As no patients were lost to follow-up, data on one-year mortality were available in all 4670 patients. A total of 252 patients (5.4%) died between 2 days and one year after admission. Mean CK in patients who died within one-year was 3268 U/L (SD 2461) compared to 2273 U/L (SD 1966) in those who survived (p <0.001). Mean CK-MB was 359 U/L (SD 268) in those who died within one year, compared to 238 U/L (SD 202) in patients who were alive after one year (p <0.001). Survival curves of patients in the different CK or CK-MB tertiles are depicted in figure 2 and figure 3. Patients in the highest tertile of CK had an increased risk of one-year mortality, HR 2.3 (95% CI 1.77-2.90) compared to those in the other tertiles. However, one-year mortality was not different between patients in the two lower tertiles of CK (p=0.59). Patients in the highest tertile of CK-MB had also an increased one-year mortality, HR 2.41 (95% CI 1.88–3.09). In the two lower tertiles of CK-MB, there was also no significant difference in one-year mortality (p=0.97).

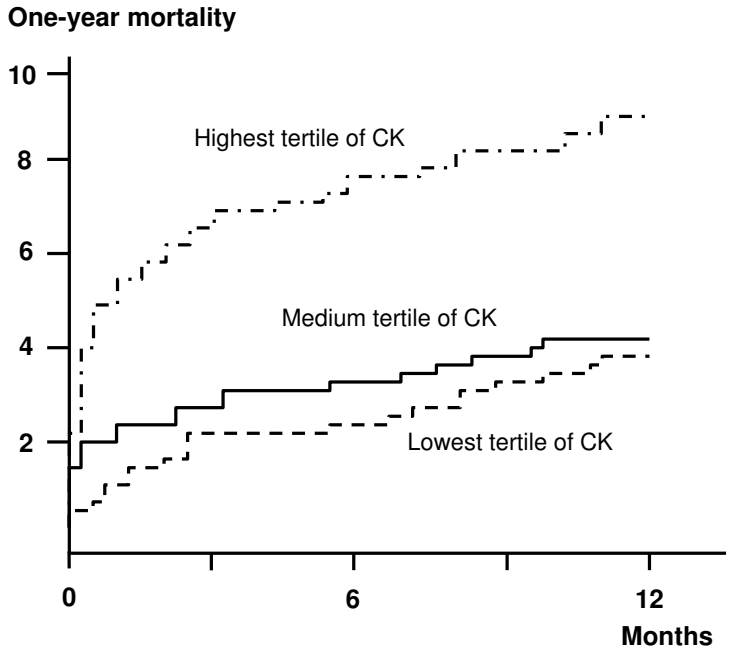


**Figure 2.** One-year mortality according to tertiles of peak CK in 4670 pts who survived at least 2 days after primary PCI for ST-elevation MI, p <0.001 for the highest tertile as compared to the lower tertiles.

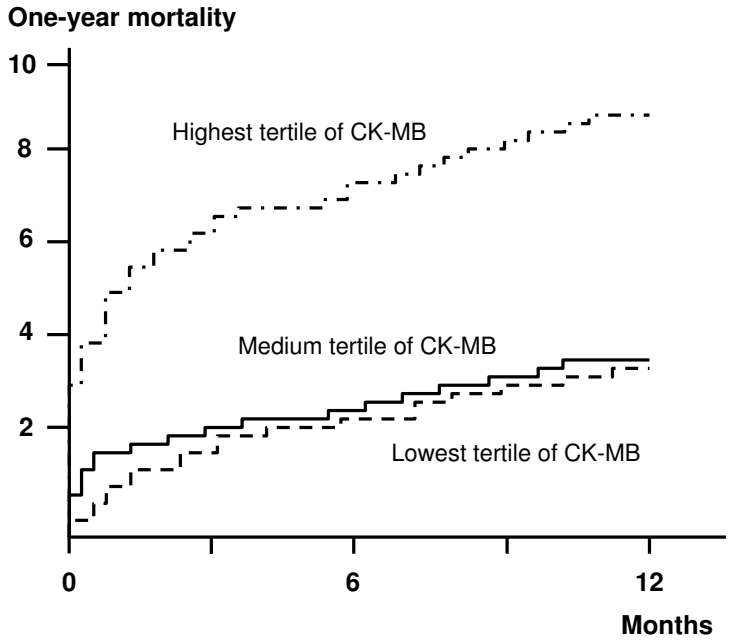


**Figure 3.** One-year mortality according to tertiles of peak CK-MB in 4670 pts who survived at least 2 days after primary PCI for ST-elevation MI, p <0.001 for the highest tertile as compared to the lower tertiles.

*Multivariable analyses*

In 2738 patients, the unadjusted HR for developing a low LVEF was 5.76 (95% CI 4.51-7.35) of patients in the highest tertile of CK and 5.49 (95% CI 4.31-6.99) of patients in the highest tertile of CK-MB. After adjusting for age, gender, infarct location, Killip classification on admission, previous MI, stent implantation, multivessel disease and TIMI flow post PCI, the HR in patients in the highest tertile of CK was 4.61 (95% CI 3.48-6.09) and of patients in the highest tertile of CK-MB 4.35 (3.31-5.74).

After adjusting for differences in age and gender in the total study group of 4670 patients, both patients in the highest tertile of CK, HR 1.79 (95% CI 1.52–2.10) and the highest tertile of CK-MB, HR 1.71 (95% CI 1.46–2.01) had an increased one-year mortality. After adjusting for differences in age, gender, infarct location, Killip classification on admission, multivessel disease, previous MI, stent implantation and TIMI flow post PCI, the HR in patients in the highest CK tertile was 2.06 (95% CI 1.54–2.76) and of patients in the highest CK-MB tertile 2.16 (95% CI 1.61–2.90). If was also adjusted for LV ejection fraction in patients where

LVEF was available (n=2738), the HR of one-year mortality in patients in the highest tertile of CK was 2.28 (95% CI 1.32-3.91) and of patients in the highest tertile of CK-MB 1.91 (95% CI 1.11-3.26) (figure 4).

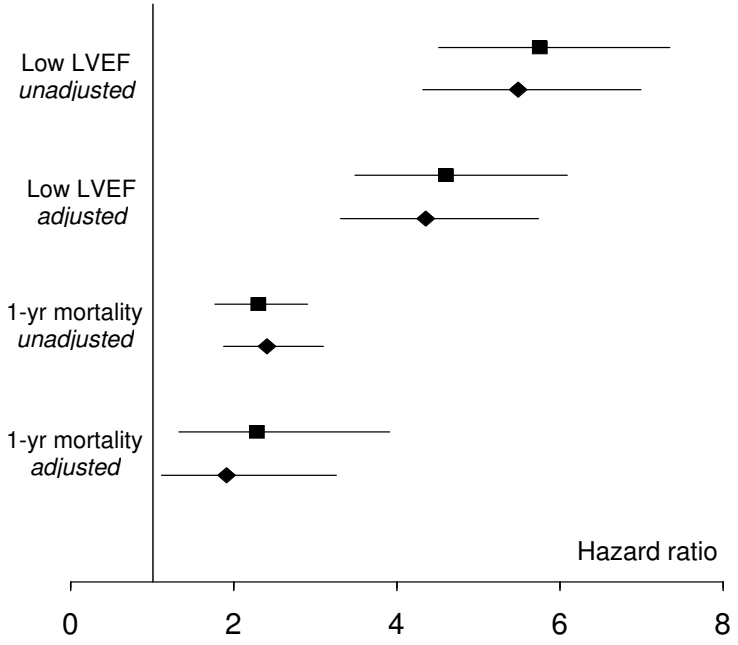


**Figure 4.** Adjusted and unadjusted hazard ratios (95% CI) for 1-yr mortality or a low LV ejection fraction in pts in the highest tertiles of CK(■) and CK-MB (♦) as compared to the lower tertiles.

## Discussion

The present study shows that both peak CK and peak CK-MB are comparable independent predictors of LV ejection fraction and one-year mortality in patients after primary PCI for STEMI. Furthermore, particularly patients in the highest tertiles of either CK or CK-MB had a poor prognosis, whereas the differences between the lower tertiles were less clear.

*Previous literature*

Since the 1970's, the association between peak CK, infarct size and mortality has been recognized [1,2]. Although some doubt was raised about the association

between CK and long-term mortality in some studies [3,4], the association was confirmed for several types of acute coronary syndromes (ACS), including patients without ST-segment elevation and patients treated with thrombolytic therapy [5].

After recognition of the importance of CK, the additional significance of the isomer CK-MB was identified [6,7,16]. In a large trial was shown that in patients with ACS without ST-segment elevation, minor elevations of CK-MB were related to increased mortality [17]. Moreover, also CK-MB elevation without concomitant CK elevation was associated with a worse prognosis [18,19].

Although most of the previous studies showing the significance of CK(-MB) after MI are large-scale and incontrovertible, they are performed in patients with non-ST-elevation ACS or STEMI for which thrombolytic or no reperfusion therapy was given. Theoretically, restoration of antegrade blood flow may influence the amounts of biomarkers release. Of the total CK in the myocardial infarct area, approximately 15% reaches the circulation in the absence of coronary recanalization. The remainder is hydrolysed either locally or in lymph [20]. As long as a predictable relationship exists between the amount of CK depleted and the amount that reaches the circulation, serial samples offer an estimate of the amount depleted and, therefore, an estimate of infarct size. But in animal models, reperfusion within 2 hours after coronary occlusion doubles the ratio of the amount of enzyme that is in the plasma compared with that depleted from myocardium [21]. Consequently, comparisons between reperfused and nonreperfused patients can be problematic [22]. Another study suggested also that CK-MB might overestimate infarct size after reperfusion [23].

However, as our analyses show, also in the era of primary PCI where TIMI-3 flow is achieved in the majority of patients, peak CK and CK-MB are still related to mortality and infarct size. Furthermore, in our analysis TIMI-3 flow after the primary PCI was more often observed in patients in the lower tertiles of CK and CK-MB.

*Primary PCI*

Only 2 large-scale studies on prognostic importance of biomarkers were performed in patients undergoing primary PCI for STEMI. One-year mortality was well predicted by the cumulative extent of LDH in one study [12]. But, because of the slow release into the circulation compared to CK(-MB), cumulative LDH is not a very practical alternative and therefore not widely used for this purpose. Halkin et al showed that peak CK is an independent predictor of one-year mortality in a

post hoc analysis of the CADILLLAC trial [13]. This trial had several in- and exclusion criteria, influencing the external validity of the findings. Furthermore, only 73% of the included patients had available CK values, resulting in a selected group of patients with STEMI.

*Non-traditional markers*

After the redefinition of MI, troponin is the preferred biomarker to use in patients with (suspected) ACS [24]. Although there is some evidence that troponin can estimate infarct size [25], only studies with a limited sample size in patients following primary PCI have been performed, without reliable information in predicting mortality [26,27]. Myoglobin is rapidly released in the circulation and early estimation of the total extent of myocardial injury can be done, but because of the lack of cardiospecificity this marker is not used widely [28].

*Study limitations*

Several limitations on our study have to be noted. During the 13 years of inclusion, techniques of PCI and medical treatment afterwards have been changed. This may have affected outcome, but seems to be unlikely affecting our principal conclusions. Although blood samples were taken every 8 hours, we did not calculate the area under the CK and CK-MB curve, another possible predictor of mortality after MI [7,8]. Furthermore, data on time to peak CK(-MB) are lacking. Moreover, as we collected blood samples until 24 hours after baseline and some patients might have their biomarker peak after this time window, possibly underestimating of peak CK(-MB) might have occurred in some patients. However, this seems to be unlikely, also according to others [13]. Finally, as a central role has been propagated last years for the cardiac troponins [24], these specific biomarkers potentially might have even more significance after primary PCI for STEMI [22].

*Conclusion*

Our study shows an independent association between either peak CK or CK -MB and both LV function and mortality in patients undergoing primary PCI. Accordingly, the worldwide use of these two biomarkers seems to be justified, also in patients with TIMI-3 flow after mechanical reperfusion therapy. Future efforts should be aimed towards how to improve treatment in high-risk patients, as identified by peak CK(-MB).

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# Chapter 8

# Comparative predictive value of infarct location, infarct size and ejection fraction after primary PCI for ST elevation myocardial infarction

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**Submitted**

**ABSTRACT**

**Background:** Although infarct location may predict prognosis after primary percutaneous coronary intervention (PCI) for ST elevation myocardial infarction (MI), previous studies were too small to demonstrate whether this association is independent of enzymatic infarct size or left ventricular ejection fraction (LVEF).

**Methods:** A large scale, prospective, observational study was performed recording individual data from all patients who underwent primary PCI between 1991 and 2004. Stratified analyses were performed according to enzymatic infarct size. The independent association between infarct location and one-year outcome, was compared with the prognostic importance of enzymatic infarct size and LVEF.

**Results:** Of 4990 patients, 2485 (49.8%) had an anterior infarction. Patients with anterior MI had a significantly larger enzymatic infarct size (peak CK 2960 vs 2009 U/l, p <0.001) and a lower mean LVEF (40.0% vs 50.0%, p <0.001). In all tertiles of enzymatic infarct size, patients with anterior MI had a lower LVEF. Mortality within one year was higher in patients with anterior infarction as well as in those with a high enzymatic infarct size or a low LVEF. Also, in all tertiles of enzymatic infarct size, patients with anterior infarction had a higher one-year mortality. After multivariable analyses, patients with anterior infarction still had an increased risk of a high enzymatic infarct size, a poor left ventricular function and also a higher one-year mortality, OR 1.35 (95%CI 1.07-1.70). However, low LVEF was a significant stronger predictor of one-year mortality, OR 4.4 (95%CI 2.4-7.8), compared to infarct size, OR 2.0 (95%CI 1.6-2.5) or anterior location, OR 1.6 (95%CI 1.3-2.0).

**Conclusion:** After primary PCI, location of infarction is still an important independent predictor of high enzymatic infarct size, low LVEF and increased mortality, even after adjusting for several clinical characteristics. However, LV ejection fraction is a stronger predictor of one-year mortality.

## Introduction

In the pre-fibrinolytic and fibrinolytic era, it was shown that myocardial infarction (MI) involving the anterior wall was associated with increased myocardial cell death, reduced left ventricular (LV) ejection fraction and worse prognosis [1-4]. Apart from an increased amount of myocardial cell death after anterior infarction, also other factors may influence myocardial function and worse outcome in these patients [5-7], but most previous studies were too small to demonstrate the independent effect on prognosis of anterior MI.
Primary percutaneous coronary intervention (PCI) has improved prognosis after ST elevation myocardial infarction (STEMI), particularly after anterior MI [8,9]. In patients undergoing primary PCI, the association between enzymatic infarct size and prognosis as well as between LV ejection fraction and prognosis was previously demonstrated [10,11]. Only one study examined in detail the impact of infarct location on prognosis after primary PCI, and this concerned an ad hoc analysis of data of a clinical trial, with many inclusion and exclusion criteria [7]. Therefore, the question remains whether infarct location is still an important predictor of mortality after primary PCI, particularly if compared with the prognostic importance of infarct size and LV-function. The primary aim of the present study was to evaluate whether location of MI has independent influence on prognosis after primary PCI, and to compare this with enzymatic infarct size and LV-function.

## Methods

*Population*
From January 1991 to December 2004, individual data from all patients with admission diagnosis of STEMI admitted for primary PCI at the Isala klinieken (Zwolle, the Netherlands) were prospectively recorded. To avoid double inclusion of patients, only the first recorded admission for STEMI during the study period was used. Patients were diagnosed with STEMI if they had chest pain of > 30 minutes' duration with ST segment elevation > 2 mm in at least 2 precordials and > 1 mm in the limb leads. Before the primary PCI procedure, all patients received 500 mg of aspirin intravenously, and 5000 IU intravenous heparin. Primary PCI was performed with standard techniques if the coronary anatomy was suitable for angioplasty. PCI success was determined by the classification system of the

Thrombolysis in Myocardial Infarction (TIMI) trial, in which a grade 3 blood flow indicates normal flow within the vessel, in combination with a myocardial blush grade 2 and 3 [12]. Additional treatment with glycoprotein IIb/IIIa-inhibitors or stents was at the discretion of the treating cardiologist. All patients were treated with optimised drug-therapy including angiotensin-converting enzyme inhibitors, β-blockers, aspirin and lipid-lowering drugs where appropriate. During the observational period, none of the patients was treated with a prophylactic implantable defibrillator.

*Measurements*

The infarct location was categorized into two groups: anterior location and non-anterior location according to the admission electrocardiogram. Patients with a new left bundle branch block were classified as anterior MI. Protocol-specified blood sampling for creatine kinase (CK) and the muscle-brain fraction (CK-MB) levels was performed at baseline and at 8 hours, 16 hours and 24 hours after the index PCI. Measurement of serum total CK and CK-MB levels was performed according to local hospital standards. A large enzymatic infarct size was defined as patients who had CK release in the highest tertile. LV ejection fraction was measured before discharge by radionuclide ventriculography or by echocardiography if the patient had atrial fibrillation. A severely depressed LV ejection fraction was defined as an ejection fraction < 30%.

*Data collection and follow-up*

We collected the following variables from the patient files: age, gender, history of hypertension, diabetes, hyperlipidemia, and smoking, previous myocardial infarction, angiographic variables, laboratory measurements, pre-discharge LV function and discharge medication. Follow-up information was obtained from the patient's general physician or by direct telephone interview with the patient. Events were confirmed by reviewing the concerning letter to the general physician or patient’s clinical file if necessary, and all cause mortality was reported. Re-MI was defined as anginal complaints with new CK(-MB) elevation and/or new Q-waves on the electrocardiogram in follow-up. Study approval was obtained from the medical ethic committee of our hospital.

*Statistical analysis*

Statistical analysis was performed with the Statistical Package for the Social Sciences (SPSS Inc., Chicago, IL, USA) version 12.0.1. Continuous data were expressed as mean ± standard deviation and categorical data as percentage, unless otherwise denoted. Differences between continuous data were performed by students t test, and the chi-square or Fisher's exact test were used as appropriate for dichotomous data. Multivariable logistic regression analysis was performed to test the independent association between infarction location and a high enzymatic infarction size or a low left ventricular function. Peak CK levels were divided into three equal tertiles to determine the prognostic importance of infarct location in infarctions of different enzymatic size. As anterior MI was present in almost half of patients, the medians of enzymatic infarct size and LV ejection fraction were used to compare the association between infarct location, enzymatic infarct size, LV ejection fraction and prognosis. Significant variables analyzed are reported with their respective odd ratios and 95% confidence intervals (CI). Cox proportional-hazards regression models were used to estimate hazard ratios of infarction location with regard to survival at one year. For all analyses, statistical significance was assumed when the two-tailed probability value was $< 0.05$.

## Results

*Baseline characteristics*

During the study period, 5030 patients were included. Data on infarct location were available in 4990 patients (99%) and these patients were the study population. Mean age was 61.2 ± 11.9 years (range 19-94 years) and 24% were female. Data on enzymatic infarct size were available in 4820 patients (97%) and on left ventricular ejection fraction in 2861 patients (57%). The mean ischemic time before admission was 3.9 ± 4.8 hours. Diabetes was documented before admission in 535 patients (10.8%). A total of 2485 patients (49.8%) had an anterior infarction. Differences of the baseline and treatment characteristics between patients with anterior infarct location and those with non-anterior infarct location are summarized in tables 1 and 2.

**Table 1:** Baseline characteristics according to infarct location in 4990 pts who were admitted for primary PCI for ST-elevation MI.

| Variables | Anterior n = 2485 | Non-anterior n = 2505 | p-value |
|---|---|---|---|
| Age, yr | 61.0±12.2 | 61.5±11.5 | 0.17 |
| Female gender | 23.0 | 24.6 | 0.17 |
| *History of* | | | |
| MI | 12.2 | 12.9 | 0.72 |
| CABG | 1.8 | 4.0 | < 0.001 |
| PCI | 5.1 | 7.0 | 0.02 |
| Stroke | 3.6 | 3.1 | 0.60 |
| Hypertension | 29.3 | 28.1 | 0.63 |
| Hyperlipidemia | 18.6 | 23.1 | < 0.001 |
| Family CVD | 41.3 | 42.6 | 0.66 |
| Smoke | 48.7 | 48.8 | 0.71 |
| Diabetes | 11.5 | 10.1 | 0.31 |
| Referred from other hospital | 51 | 33 | < 0.001 |
| Killip class >1 | 12.9 | 8.6 | < 0.001 |
| Patient delay, hr | 4.0±5.1 | 3.7±4.5 | 0.02 |
| Door to balloon time <30 minutes | 53 | 41.7 | < 0.001 |
| *Coronary angiography* | | | |
| Multi-vessel disease | 48.0 | 59.6 | < 0.001 |
| TIMI 0 flow pre-PCI | 59 | 66 | < 0.001 |
| Collaterals, Rentrop >0 | 41.8 | 50.2 | < 0.001 |
| Diameter infarct related vessel (mm) | 2.8±0.50 | 3.1±0.55 | < 0.001 |

% or mean ± sd

**Table 2.** Treatment according to infarct location in 4990 pts who were admitted for primary PCI for ST-elevation MI.

| Variables | Anterior n = 2485 | Non-anterior n = 2505 | p-value |
|---|---|---|---|
| *Initial treatment* | | | |
| Primary PCI | 90.5 | 92.5 | 0.01 |
| Conservative | 5.3 | 4.5 | 0.2 |
| CABG | 4.3 | 3.0 | 0.02 |
| TIMI 3 flow post-PCI | 85 | 89 | < 0.001 |
| Hospital stay (days) | 5.3±6.8 | 5.1±6.2 | 0.23 |
| *Discharge medication* | | | |
| Aspirin | 87 | 94 | < 0.001 |
| Cumarins | 17.1 | 6.0 | < 0.001 |
| Beta-blocker | 81.8 | 82.5 | 0.79 |
| Diuretics | 14.6 | 9.6 | < 0.001 |
| ACE-inhibitors | 69 | 34 | < 0.001 |

% or mean ± sd

**Table 3:** Outcome according to infarct location in 4990 pts who were admitted for primary PCI for ST-elevation MI.

| Variables | Anterior n = 2485 | Non-anterior n = 2505 | p-value |
|---|---|---|---|
| Mean LVEF (%) | 40.0±12.3 | 50.0±9.5 | < 0.001 |
| LVEF < 30% | 25 | 2.9 | < 0.001 |
| Peak CK (U/L) | 2960±2926 | 2009±2191 | < 0.001 |
| Large enzym. infarct size | 42.1 | 22.6 | < 0.001 |
| Peak CK-MB (U/L) | 295±254 | 209±172 | < 0.001 |
| Mortality | | | |
| 30 days | 5.8 | 3.4 | < 0.001 |
| One year | 8.8 | 5.8 | < 0.001 |
| Re-MI or death | | | |
| 30 days | 6.5 | 3.8 | < 0.001 |
| One year | 13.2 | 9.4 | < 0.001 |
| Re-PCI | | | |
| 30 days | 6.3 | 6.1 | 0.76 |
| One year | 14.6 | 14.8 | 0.87 |
| CABG | | | |
| 30 days | 8.1 | 7.7 | 0.54 |
| One year | 13.1 | 13.2 | 0.92 |
| Stroke | | | |
| 30 days | 0.3 | 0.5 | 0.26 |
| One year | 0.9 | 1.0 | 0.91 |

% or mean ± sd

*Clinical outcome*

Patients with anterior MI had a significantly larger enzymatic infarct size and a lower LV ejection fraction (table 3). The unadjusted risk of a large enzymatic infarct size for patients with anterior location was 2.49 (95% CI 2.2 – 2.8). Also the prevalence of a severely depressed LV ejection fraction was much higher in those with anterior infarction location (25%) compared to patients with non-anterior location (2.9%). Furthermore, in all tertiles of enzymatic infarct size, patients with anterior MI had a lower LV ejection fraction (figure 1).

A total of 230 patients (4.6%) died within 30 days and 363 (7.3%) died within one year after admission. Both a large enzymatic infarct size, OR 2.1 (95% CI 1.70 – 2.60) and a severely depressed LV ejection fraction, OR 5.48 (95% CI 3.52 – 8.53) were associated with increased one-year mortality. A large enzymatic infarct size was a predictor of one-year mortality in both patients with anterior MI, OR 2.07 (95% CI 1.46 – 2.92) and in those with non-anterior MI, OR 1.91 (95% CI 1.44 – 2.53). A severely depressed LV ejection fraction was also a predictor of one-year mortality in both patients with anterior MI, OR 5.62 (95% CI 3.11 – 10.15) and those with a non-anterior MI, OR 6.84 (95% CI 2.63 – 17.83).

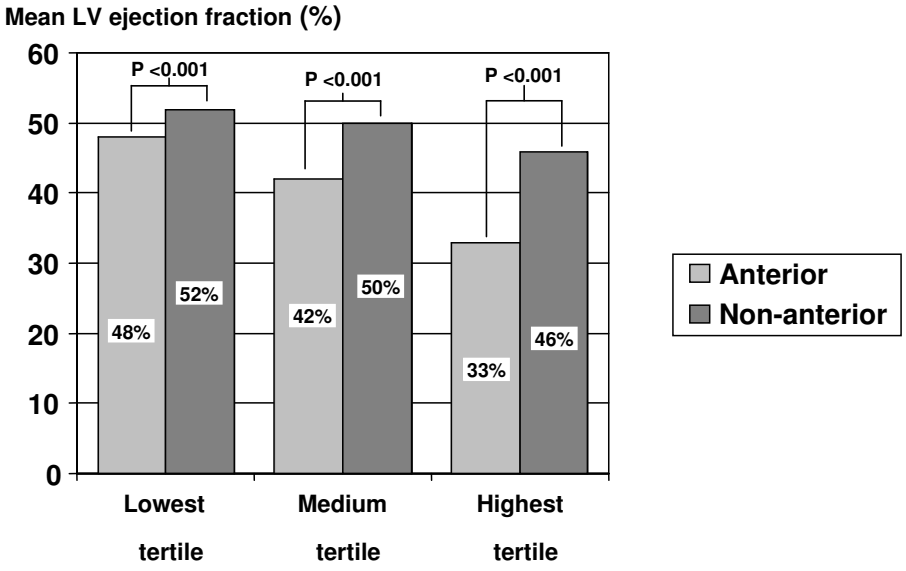


**Figure 1.** Mean LV ejection fraction in different tertiles of enzymatic infarct size according to infarct location.

One-year mortality in patients with anterior location was 8.8% compared to 5.8% in those with non-anterior infarction (p <0.001). Survival curves of patients with anterior and non-anterior infarction are depicted in figure 2.

The unadjusted risk of one-year mortality for patients with anterior location compared to non-anterior location was 1.56 (95% CI 1.26 – 1.92). The combination of death or re-MI was observed in 565 patients (11.3%) after one year. This combined endpoint was also higher in patients with anterior infarct location (table 3). Although not significant, a comparable trend for a higher mortality in patients with anterior infarction was seen in every tertile of enzymatic infarct size, as shown in figure 3.

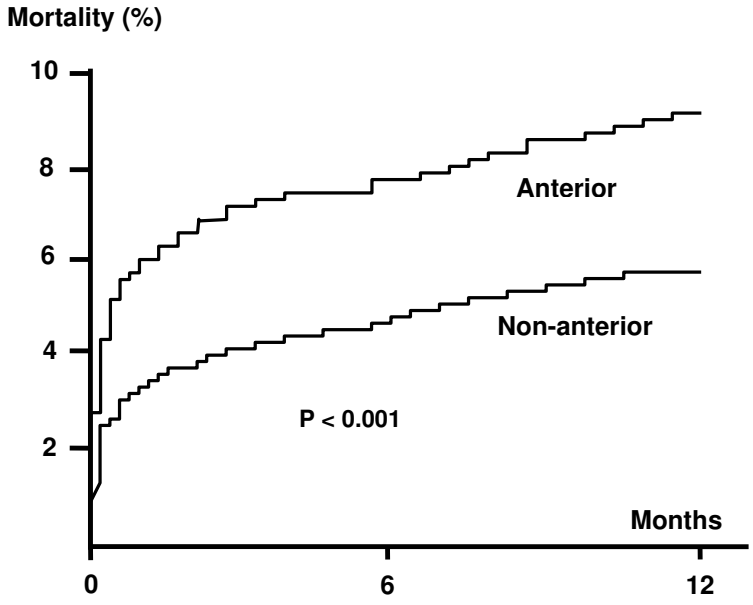


**Figure 2.** One-year mortality in 2485 patients with anterior infarct location and 2505 patients with non-anterior location.

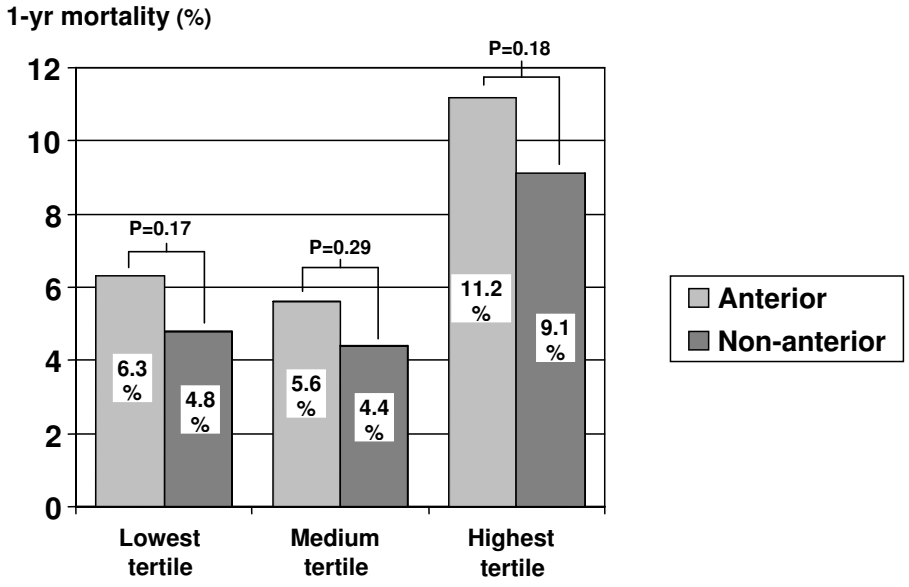


**Figure 3.** One-year mortality according to infarct location in tertiles of peak-CK in 4990 patients.

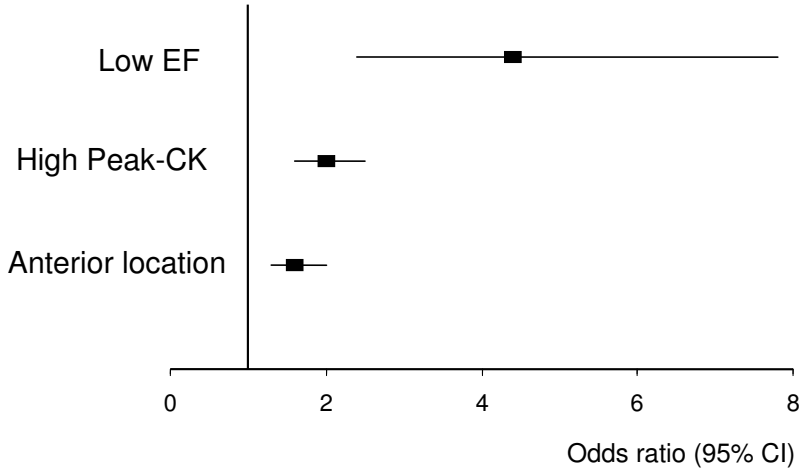


**Figure 4.** Age and gender adjusted odds ratios for one-year mortality with regard to LV ejection fraction (EF), enzymatic infarct size and infarct location in 4990 patients.

*Multivariable analyses*

After adjusting for differences in age, gender, diabetes, previous MI, heart failure on admission, hypercholesterolemia and enzymatic infarct size, patients with anterior infarct location still had an increased risk of a severely depressed LV ejection fraction, OR 10.2 (95% CI 7.2 – 14.6). After adjusting for differences in age, gender, diabetes, previous MI, heart failure on admission and hypercholesterolemia, patients with anterior infarct location had also still an increased risk of a large enzymatic infarct size, OR 2.44 (95% CI 2.14 – 2.78).

After adjusting for differences in age, gender, diabetes, previous MI, heart failure on admission, hypercholesterolemia and even enzymatic infarct size, patients with anterior infarct location had also still a significant increased risk of one-year mortality, OR 1.35 (95% CI 1.07 – 1.70).

*Comparison of prognostic importance*

To compare the prognostic importance, patients with anterior MI (50% of patients) were compared with those with a LV ejection fraction lower than the median (EF

<46%), and with those with enzymatic infarct size higher than the median (CK >1729 U/L). The odd ratios, corrected for age and gender, for one-year mortality were 1.6 (95% CI 1.3 – 2.0) of anterior location, 2.0 (95% CI 1.6 – 2.5) of enzymatic infarct size and 4.4 (95% CI 2.4 – 7.8) of LV ejection fraction, and are depicted in figure 4.

## Discussion

Our results show that in patients undergoing primary PCI for STEMI, location of infarction is still an important independent predictor of a large enzymatic infarct size, low LV ejection fraction and increased mortality, even after adjusting for several clinical characteristics. In all tertiles of enzymatic infarct size, patients with anterior MI have a lower LV ejection fraction and an increased one-year mortality. LV ejection fraction is, however, a stronger predictor of mortality compared to infarct location or enzymatic infarct size.

*Previous studies*

Several studies have investigated the relation between infarct location, infarct size, LV ejection fraction and prognosis. However, most of these studies were performed in patients treated with thrombolytics or no reperfusion therapy at all. In patients not receiving reperfusion therapy, it was demonstrated that both peak enzyme level and infarct location had a poor in-hospital and long-term prognosis [1-3,13], although the effect of infarct location on long-term prognosis has been discussed [14,15].

If enzymatic infarct size is comparable, the effects on LV function seem to be greater after anterior infarction, particularly when the apical region is involved [16].

*Primary PCI*

After primary PCI, it was shown that both enzymatic infarct size, as defined by peak CK or peak CK-MB, and LV ejection fraction were related to prognosis [10,11]. Our study confirmed these findings.

A study with gated single-photon emission computed tomography (SPECT) showed a lower LV ejection fraction for anterior infarctions than for inferior or lateral infarctions of the same extent [5]. Also in another study, left anterior descending artery (LAD)-related infarctions, when compared with non-LAD-

related infarctions, had a lower residual LV ejection fraction for a similar amount of myocardial necrosis as determined by enzymatic infarct size [6]. A post-hoc analysis of the CADILLLAC trial demonstrated an association between infarction involving the LAD and a reduced LV function, less frequent collateral flow, impaired myocardial perfusion and increased major adverse cardiac events after one year [7]. However, this trial had a number of in- and exclusion criteria, influencing the external validity of the findings, and they did not adjust for enzymatic infarct size.

A remarkable observation of a sub-analysis of the MADIT II trial was recently published, showing in patients with advanced LV dysfunction that inferior wall MI was associated with a significantly higher risk of mortality than anterior wall MI [17]. However, most patients included in MADIT II had their infarction very long before inclusion and the type of reperfusion therapy was not clear in that study. Possibly, progressive coronary artery disease with additional myocardial infarction may have contributed to the poor prognosis of inferior infarctions.

*Possible mechanisms*

There may be several reasons for the association between infarction location and prognosis. Anterior MI may be associated with a larger mass of infarcted myocardium [1]. However, both our study and previous studies [1-3,18] show also an association between location and prognosis after correction for enzymatic infarct size.

Possibly, specific intrinsic and extrinsic qualitative differences between the myocardial wall regions are important [19]. Patients with anterior MI have a greater risk of expansion, regional dilatation and thinning of the infarct zone, leading to ventricular aneurysm, which, apart from the increased risk of thrombus formation and myocardial rupture, has an adverse effect on LV function [20]. This higher risk of aneurysm may be caused by a thinner myocardial wall at the apex by less circumferential fibres of the middle myocardial layer [21]. Therefore, apical involvement may result in greater systolic dysfunction per unit area infarcted [16]. Although a patent infarct-related artery has a favourable effect on LV remodelling [22] and is achieved in the majority of patients treated with PCI [23], LV remodelling remains common after anterior MI, despite the use of angiotensin-converting enzyme inhibitors, angiotensin II receptor blockers and β-blockers [24-26].

Another possible reason for the poor prognosis after anterior MI is the potential disturbance in electromechanical behaviour, with septal incoordination after anterior MI [27]. Occurrence of bundle branch block or other intraventricular conduction defects may also influence prognosis [1,17].

Furthermore, differences in reperfusion may also explain the difference in outcome between anterior and inferior infarction. It was suggested that spontaneous reperfusion occurs more often in patients with non-anterior infarction [7], but this was not confirmed by our study. TIMI-3 flow post-PCI was more common in non-anterior MI in both our study and previous studies [7]. This and the lower prevalence of collaterals in anterior MI may contribute to less improvement in LV function [28].

*Limitations*

During the 11 years of inclusion, techniques of PCI and medical treatment afterwards have been changed. Although this may have affected outcome, it seems unlikely to affect our principal conclusions. Another limitation is the selection of patients in the first years of registry, as patients with anterior infarction were more often accepted for primary PCI from referral hospitals in that period. Our follow-up period was only one year. Furthermore, we had no data on death causes or data of medication changes during follow-up.

*Conclusion*

Although not as strong as LV ejection fraction, location of infarction is still an important independent predictor of prognosis in patients undergoing primary PCI. The question remains whether the prognosis of patients with anterior MI could be improved by more aggressive medical treatment or by using more often prophylactic implantable defibrillators.

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# Chapter 9

# Summary and conclusions

This thesis addresses the clinical value of systematic measurements of cardiac biomarkers after percutaneous coronary interventions (PCI). The importance of troponin T (TnT), creatine kinase (CK) and its muscle-brain isomer (CK-MB) is evaluated in patients undergoing elective PCI as well as in patients undergoing primary PCI for ST-elevation myocardial infarction (STEMI).

The **first chapter** starts with an introduction and overview of this thesis. The number of PCIs has increased during the past decades and research on quality control and clinical implications is mandatory.
**Part I** of this thesis is focused on myocardial injury and the measurement of cardiac biomarkers after elective PCI.
In the **second chapter**, we describe the findings of a prospective study on 713 unselected patients with elective PCI. TnT elevation (21%) occurred more often than CK elevation (9%). After a mean follow-up period of 10.9 months, postprocedural TnT, but not CK, was significantly associated with the primary combined endpoint of adverse cardiac events. In conclusion, increase of TnT after elective PCI has stronger prognostic implications when compared to increase of CK.
We assessed the influence of pre-treatment with clopidogrel on the incidence of minor postprocedural TnT elevations in the **third chapter** in a prospective, observational study on 656 patients undergoing elective PCI. TnT was elevated in 34% of the 330 patients without pre-treatment, compared to 30% of the 326 pre-treated patients. After multivariable analyses, patients who were pre-treated with clopidogrel had a significantly lower risk of postprocedural TnT elevation (OR 0.69, 95% CI 0.49-0.99). This effect was found in particular in those with older age, previous PCI, angina CCS 4 and multivessel disease. We concluded that, combined with results of other studies, pre-treatment with clopidogrel should be advised in patients waiting for elective PCI.
In the **fourth chapter** we describe that patients with elective PCI undergoing multivessel PCI, compared to those undergoing single-vessel PCI, more often had TnT elevation after PCI (31.5 vs. 18.3%, p=0.001). Furthermore, there was a higher incidence of cardiac events during a mean follow-up period of 10.9 months, in those undergoing a multivessel PCI. However, when in a multivariate model correction for the presence of multivessel disease itself was made, this association was not significant anymore. We could conclude that multivessel PCI was associated with more TnT release and that there was a trend towards a higher incidence of cardiac events during follow-up.

We present the results of a meta-analysis in the **fifth chapter**, including 20 studies involving 15,581 patients undergoing elective PCI. Overall, troponin was elevated after PCI in 32.9% of patients. After a mean follow-up period of 16.3 months, mortality was higher in patients with postprocedural troponin elevation compared to those without troponin elevation (4.4 vs. 3.3%, p=0.001). Furthermore, the combined endpoint of mortality or non-fatal myocardial infarction (MI) occurred more often in patients with troponin elevation (8.1 vs. 5.2%, p<0.001). According to this meta-analysis, troponin elevation after elective PCI provides important prognostic information.

**Part II** of this thesis is focused on myocardial injury and the measurement of cardiac biomarkers in patients treated with primary PCI.
A study investigating the value of TnT on admission in 444 patients undergoing primary PCI for STEMI is described in the **sixth chapter**. Elevation of TnT on admission was present in 47% of patients. Presentation delay, anterior MI location and higher age were independent predictors of elevated cTnT on admission. Furthermore, patients with TnT elevation on admission were less likely to have successful primary PCI compared to those without TnT elevation on admission and had significantly higher rates of one-year mortality.
The results of a study on the prognostic importance of CK and CK-MB in 4,670 patients undergoing primary PCI for STEMI are presented in the **seventh chapter**. Both increased CK and CK-MB were associated with a lower left ventricular ejection fraction (LVEF). One-year mortality was 5.4% and both peak CK and CK-MB were higher in those who died. Patients in the highest tertile of either peak CK or CK-MB had, also after multivariable analyses, a higher one-year mortality, whereas the differences between the two lower tertiles were not significant. We concluded that, in patients undergoing primary PCI, peak CK and CK-MB are independent predictors of LVEF and mortality.
In the **eighth chapter**, we assess the comparative predictive value of infarct location, infarct size and ejection fraction after primary PCI for STEMI. Low LVEF was a stronger predictor of one-year mortality (OR 4.4) compared to enzymatic infarct size (OR 2.0) or anterior location (OR 1.6). In addition, even after correction for enzymatic infarct size in multivariable analyses, patients with anterior infarction still had an increased risk of a poor LVEF and also a higher one-year mortality. In conclusion, although not as strong as LVEF, infarct location remains an important independent predictor of prognosis in patients after primary PCI.

## Final comments

Many patients with coronary artery disease are nowadays treated with PCI and it is the most frequently performed revascularisation therapy [1]. The number of PCIs is still rising over the last years, and a further growth may be expected [2]. The recently published COURAGE trial showed no difference in the occurrence of major cardiovascular events in follow-up between an initial interventional approach compared to an initial conservative strategy in patients with stable angina pectoris [3]. However, this seems to be a very low-risk population, as most patients had minimal or no angina, a well preserved LVEF, and patients with a markedly positive stress test were excluded. Also, an improvement in angina-free status and a reduction in the requirement for subsequent revascularisation was observed in the patients in the interventional arm in that study [4]. As improving quality of life, and not improving survival, was already the main reason for performing PCI in patients with stable angina, this trial will probably not have many influence on the number of PCIs in these patients. Moreover, since invasive treatment has been shown to improve prognosis in patients with ST-elevation acute coronary syndromes (ACS) [5] as well as non-ST-elevation ACS [6], and the fact that there still seems to exist a risk-averse instead of a risk-driven strategy in daily practise in patients with ACS [7], the expected further rise in the total number of PCI, in particular performed for acute coronary syndromes, seems plausible.

### *Elective PCI*

Since the primary goal of elective PCI is to improve quality of life, particularly by reducing anginal complaints, it is important to reduce complications and side-effects to a minimum. STEMI occurs rarely in patients undergoing elective PCI, with reported rates of less than 0.5% [8], but is a serious complication, and the development of new Q-waves has been associated with a worse prognosis [9]. Non-STEMI after elective PCI is more common and is also related to cardiac events during follow-up. This has been shown for minor myocardial injury, as measured by elevations of CK(-MB) and especially troponin according to our analyses.

The measurement of postprocedural biomarker release, especially elevation of troponin, seems therefore suitable to monitor PCI success when applying new techniques and medications. Reduced postprocedural biomarker release has

been shown after treatment with glycoprotein IIb/IIIa inhibitors [10,11], clopidogrel [12], statins [13] or adenosine [14].
Whether patients with postprocedural biomarker release might benefit of more aggressive medical therapy (e.g. increasing or adding beta-blockers, ACE-inhibitors and/or lipid-lowering drugs) or a lower threshold for re-angiography, has to be investigated.

***Primary PCI***

Apart from the ECG at admission, cardiac enzymes and especially troponin at admission are helpful to identify patients with a worse prognosis in those undergoing primary PCI for STEMI [15,this thesis]. This can be in part explained by a longer delay in these patients, and early diagnosis and reperfusion therapy are very important. Efforts to improve prognosis of patients with increased TnT at admission should be made, and the use of glycoprotein IIb/IIIa inhibitors for instance has been associated with improved myocardial perfusion in patients with elevated troponin levels at admission and TIMI-3 flow post-PCI [16].
According to this thesis, peak values of CK and CK-MB predict prognosis in patients treated with primary PCI. Therefore, these enzymes may stratify patients for additional therapies. For example, cardiac enzymes might be superior, possibly next to LVEF, infarct location and other variables, in selecting patients with potential benefit of implantable defibrillators, whereas a low LVEF is nowadays practically the only used criterion [17].
The cardiac troponins are potentially superior again, when compared to CK(-MB), in estimating infarct size and especially predicting prognosis in patients undergoing primary PCI. However, limited studies have been performed on this issue, focusing on late, single values of troponin [18,19]. Therefore, further research is warranted, with attention to the peak values of troponin.

***Other biomarkers***

Brain natriuretic peptides (BNP and/or NT-pro-BNP) are helpful for the detection of congestive heart failure [20]. Although elevations of BNP are prognostic for death in patients with ACS, and women presenting with normal troponin but elevated BNP values may benefit from early PCI [21], the preferred strategy in the individual patient with ACS remains unclear [22]. The admission value of BNP has been reported to be an independent predictor of short-term death and angiographic success after PCI in patients with STEMI [23]. Furthermore, pre-

procedural BNP in patients undergoing PCI for stable angina or non-ST-elevation ACS provides independent prognostic information during follow-up [24]. Moreover, postprocedural BNP has recently been associated with postprocedural CK-MB as well as with TnT levels, probably as a result of hemodynamic stress [25]. Whether a rise of BNP after elective PCI is also associated with prognosis has yet to be investigated.

C-reactive protein (CRP) levels have been associated with the extend of inflammatory state of atherosclerosis in patients with coronary artery disease. In patients with stable coronary disease or acute coronary syndromes, CRP measurement may be useful as an independent marker for assessing likelihood of recurrent events [26]. CRP has been related to infarct size and mortality after primary PCI for STEMI [18]. However, after multivariable analysis only troponin level and Killip-class were independent predictors of mortality in that study. Increase of CRP level after elective PCI may also have prognostic value [27,28].

Heart-type fatty acid binding protein (H-FABP) is a promising biomarker that is released rapidly from the cardiomyocyte in response to myocardial injury. It has comparable kinetics and release as myoglobin, but is more cardiospecific [29]. Recently, H-FABP was shown to provide significant incremental information for risk stratification in patients with ACS, independent of troponin, BNP and myoglobin [30]. H-FABP can be used as a marker of reperfusion success in STEMI patients treated with thrombolytics [31], as well as in patients undergoing primary PCI [32]. There are no data on the prognostic value of H-FABP after elective PCI. Possibly, it can be useful in patients who are planned to be discharged early, although it has been suggested that this can be safe using only patient symptoms, angiographic results and ECG, without biomarkers as selection criteria [33]. Future studies should demonstrate potential benefits of this biomarker.

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# Chapter 10

# Samenvatting en conclusies

In dit proefschrift wordt het belang van myocardiale schade rondom percutane coronaire interventies (PCI) onderzocht. De waarde van de cardiale markers troponine T (TnT), creatine kinase (CK) en diens MB-isomeer (CK-MB) wordt geëvalueerd bij zowel patiënten die electieve PCI procedures ondergaan, als bij patiënten die primaire PCI ondergaan vanwege een ST-elevatie myocardinfarct (STEMI).

Het **eerste hoofdstuk** geeft een algemene inleiding en beschrijft de inhoud van het proefschrift. Het aantal PCI's is de laatste decennia sterk toegenomen en onderzoek met betrekking tot kwaliteitscontrole en klinische consequenties is noodzakelijk.
**Deel I** van dit proefschrift is gericht op myocardiale schade en stijging van cardiale markers na een geplande PCI.
In het **tweede hoofdstuk** worden de resultaten van een prospectieve studie met 713 ongeselecteerde patiënten beschreven die een electieve PCI ondergingen. Na de procedure was er vaker stijging van TnT (21%) dan van CK (9%). Na gemiddeld 11 maanden bleek een postprocedurele stijging van TnT, maar niet van CK, significant geassocieerd met het gecombineerde primaire eindpunt van ongunstige cardiale gebeurtenissen. Op grond hiervan werd geconcludeerd dat stijging van TnT na een electieve PCI meer prognostische betekenis heeft in vergelijking met stijging van CK.
In een prospectieve, observationele studie met 656 patiënten die een electieve PCI kregen, onderzochten wij de invloed van voorbehandeling met clopidogrel op het voorkomen van lichte postprocedurele TnT-stijging, en beschrijven dit in het **derde hoofdstuk**. TnT was verhoogd bij 34% van de 330 patiënten zonder voorbehandeling versus 30% van de 326 patiënten met voorbehandeling. Na multivariabele analyse bleek dat patiënten die werden voorbehandeld met clopidogrel een significant lagere kans hadden op postprocedurele TnT-stijging. Dit effect werd met name gevonden bij patiënten die ouder waren, reeds eerder een PCI ondergingen, instabiele angina pectoris of meervatslijden hadden. Wij concludeerden dat, mede gezien de resultaten van andere studies, voorbehandeling met clopidogrel geadviseerd zou moeten worden bij patiënten die wachten op een electieve PCI.
In het **vierde hoofdstuk** beschrijven wij dat patiënten die een electieve PCI van meerdere vaten ondergingen, vaker TnT-stijging na de procedure hadden in vergelijking met patiënten die een electieve PCI van één vat ondergingen (31.5 vs. 18.3%). Bovendien hadden patiënten, na een PCI van meerdere vaten, vaker

ongunstige cardiale gebeurtenissen na een follow-up duur van gemiddeld 10.9 maanden, alhoewel bleek dat wanneer er gecorrigeerd werd voor meervatslijden dit verschil niet meer significant was. Wij concludeerden dat PCI van meerdere vaten geassocieerd is met vaker TnT-stijging na de procedure en een verhoogd risico op ongunstige cardiale gebeurtenissen.
We presenteren in het **vijfde hoofdstuk** de resultaten van een meta-analyse van 20 studies met in totaal 15.581 patiënten die een electieve PCI ondergingen. Troponine was verhoogd na de procedure bij 32.9% van de patiënten. Na een gemiddelde follow-up periode van 16.3 maanden was de mortaliteit hoger bij patiënten met een verhoogd troponine in vergelijking met patiënten zonder een verhoogd troponine na de procedure (4.4 vs. 3.3%). Bovendien was het gecombineerde eindpunt van mortaliteit en/of myocardinfarct in follow-up vaker behaald bij patiënten met een verhoogd troponine (8.1 vs. 5.2%). Volgens deze meta-analyse levert troponine na een electieve PCI belangrijke prognostische informatie.

**Deel II** van dit proefschrift is gericht op myocardiale schade en het bepalen van cardiale markers bij patiënten die behandeld worden met primaire PCI vanwege STEMI.
In het **zesde hoofdstuk** wordt een studie met 444 patiënten beschreven waarbij gefocust werd op de eerst gemeten TnT bij opname. Een verhoogd TnT bij opname werd gevonden bij 47% van de patiënten. Een late presentatie, voorwandinfarct en een oudere leeftijd waren onafhankelijke voorspellers van een verhoogd TnT bij opname. Bovendien hadden patiënten met een verhoogd TnT bij opname, in vergelijking met diegenen met een normaal TnT bij opname, minder vaak een succesvolle primaire PCI en een verhoogde één-jaarsmortaliteit.
De prognostische waarden van CK en CK-MB werden onderzocht in een studie met 4670 patiënten die een primaire PCI ondergingen wegens een STEMI, zoals beschreven wordt in het **zevende hoofdstuk**. Zowel een verhoogd CK als een verhoogd CK-MB waren geassocieerd met een lagere linker ventrikel ejectiefractie (LVEF). De totale één-jaarsmortaliteit was 5.4%, en zowel de piek CK als de piek CK-MB waren hoger bij diegenen die overleden. Patiënten in het hoogste tertiel van zowel piek CK als piek CK-MB hadden, ook na multivariabele analyse, een hogere één-jaarsmortaliteit, terwijl de verschillen tussen de twee lagere tertielen niet significant waren. Wij concludeerden dat bij patiënten die een primaire PCI ondergaan, piek CK en piek CK-MB beide onafhankelijke voorspellers zijn van LVEF en mortaliteit.

In het **achtste hoofdstuk** werd de prognostische waarde van infarctlocatie, infarctgrootte en LVEF na een primaire PCI bestudeerd. Een lage LVEF was een duidelijkere voorspeller van één-jaarsmortaliteit (OR 4.4) in vergelijking met enzymatische infarctgrootte (OR 2.0) en voorwandlocatie (OR 1.6). Daarnaast bleek dat patiënten met een voorwandinfarct, ook na correctie voor enzymatische infarctgrootte, een verhoogde kans hadden op het ontwikkelen van een slechte LVEF en een verhoogde één-jaarsmortaliteit. Concluderend blijkt infarctlocatie, alhoewel niet zo krachtig als LVEF, een belangrijke onafhankelijke voorspeller te zijn van de prognose van patiënten die een primaire PCI ondergaan vanwege een STEMI.

**Slotopmerkingen**

Veel patiënten met coronaire hartziekte worden tegenwoordig behandeld met een PCI en dit is tevens de meest gebruikte coronaire revascularisatie-behandeling. Het aantal verrichte PCI's neemt de laatste jaren nog steeds toe en een verdere toename wordt verwacht. Het recent gepubliceerde COURAGE onderzoek liet geen verschil zien, in harde cardiale eindpunten gedurende follow-up, tussen aanvankelijk conservatief in vergelijking met aanvankelijk invasief behandelde patiënten met stabiele angina pectoris. Doch de patiëntengroep van deze studie betreft een zeer lage risicopopulatie, daar de meeste patiënten geen of slechts geringe angina pectoris klachten hadden, een goede LVEF hadden en patiënten met een sterk positieve inspanningstest geëxcludeerd werden. Bovendien bleken de patiënten in de aanvankelijk invasief behandelde groep wel vaker vrij te blijven van angina pectoris en minder vaak revascularisatie-behandelingen in de follow-up periode nodig te hebben. Omdat verbetering van de kwaliteit van leven en niet verlenging van de levensduur al de voornaamste reden is om een electieve PCI te verrichten, zal deze studie het jaarlijks aantal verrichte PCI's waarschijnlijk niet sterk beïnvloeden. De levensverwachting van patiënten met zowel ST-elevatie als non-ST-elevatie acute coronaire syndromen (ACS) kan wel verbeterd worden met een invasieve behandeling. Daar ook gebleken is dat patiënten met een ACS nog steeds te weinig invasief behandeld worden, lijkt de verwachte verdere stijging van het aantal jaarlijks te verrichten PCI's aannemelijk, vooral voor behandeling van patiënten met een ACS.

***Electieve PCI***

Aangezien het belangrijkste doel van een electieve PCI verbeteren van de kwaliteit van leven is, vooral door het verminderen van angineuze klachten, is het belangrijk om complicaties en bijwerkingen van de interventie tot een minimum te beperken. Er ontstaat zelden een STEMI als gevolg van een electieve procedure (ca 0.5%), maar het is een ernstige complicatie en het ontstaan van Q-golven op het ECG is geassocieerd met een slechte prognose. Non-STEMI ontstaat vaker na een electieve PCI en is ook geassocieerd met cardiale gebeurtenissen in follow-up. Dit is bewezen voor geringe myocardiale schade zoals bepaald met CK(-MB) en ook voor troponine zoals onze analyses laten zien.

Het meten van postprocedurele enzymuitstoot, vooral de verhoging van troponine, lijkt daarom bruikbaar om het succes van een PCI te beoordelen als er een nieuwe techniek toegepast of medicatie gebruikt wordt rondom een PCI. Het zou ook gebruikt kunnen worden voor kwaliteitscontrole. Verlaging van de postprocedurele enzymuitstoot is gezien bij gebruik van glycoproteine IIb/IIIa remmers, clopidogrel, statines en adenosine.

Of patiënten met minimale myocardiale schade na een electieve PCI ook baat hebben bij een agressievere medicamenteuze behandeling of een lagere drempel voor re-angiografie, moet nog onderzocht worden.

***Primaire PCI***

Van de patiënten die een primaire PCI vanwege STEMI ondergaan, zijn naast het ECG ook cardiale enzymen en met name troponine bij opname in staat om patiënten met een slechtere prognose te identificeren. Dit kan deels verklaard worden door een latere presentatie, en vroege diagnose en reperfusietherapie zijn erg belangrijk. Pogingen om de prognose van patiënten met een verhoogd troponine bij opname te verbeteren zijn nodig. Het gebruik van glycoproteine IIb/IIIa remmers is bijvoorbeeld al geassocieerd met een betere myocardiale perfusie bij patiënten met een verhoogd troponine (bij opname) en TIMI-3 flow na de procedure.

Volgens dit proefschrift voorspellen piekwaarden van CK en CK-MB de prognose van patiënten die behandeld zijn met een primaire PCI. Deze enzymen zijn daarom mogelijk bruikbaar om patiënten te stratificeren naar aanvullende behandelingen. Wellicht zijn cardiale enzymen, in combinatie met infarctlocatie, LVEF en andere variabelen, superieur bij het selecteren van patiënten met een voordeel van het implanteren van defibrillatoren, terwijl thans in de praktijk een lage LVEF bijna het enige gebruikte selectiecriterium is.

Cardiale troponines zijn mogelijk opnieuw superieur om, in vergelijking met CK(-MB), infarctgrootte in te schatten en met name in het voorspellen van de prognose van patiënten die een primaire PCI ondergaan. Tot nu toe is er slechts een beperkt aantal studies gepubliceerd waarbij bovendien slechts één enkele late bepaling van troponine werd onderzocht. Daarom is verder onderzoek noodzakelijk met betrekking tot dit onderwerp, met ook aandacht voor de piekwaarden van troponine.

***Andere cardiale markers***

Het brain natriuretisch peptide (BNP) is bruikbaar bij het opsporen van hartfalen. Alhoewel verhogingen van het BNP ook prognostische betekenis hebben bij patiënten met een ACS, is het nog onduidelijk in hoeverre het de behandeling van de individuele patiënt met een ACS kan beïnvloeden. Het BNP bij opname is bij patiënten met een STEMI een onafhankelijke voorspeller van overlijden op korte termijn en angiografisch succes na een primaire PCI. Bovendien kan de pre-procedurele waarde van het BNP ook prognostische informatie geven over patiënten die een PCI ondergaan vanwege stabiele angina pectoris of een non-ST-elevatie ACS. Tevens is het postprocedureel BNP geassocieerd met zowel postprocedurele CK-MB als met TnT waarden, waarschijnlijk als gevolg van veranderingen in de hemodynamiek. Of een stijging van het BNP na een electieve PCI ook prognostische waarde heeft, moet nog worden onderzocht.

C-reactief proteïne (CRP) is geassocieerd met de uitgebreidheid van de ontsteking bij atherosclerose van patiënten met een coronaire hartziekte. Zowel bij patiënten met stabiele coronaire hartziekte als bij diegenen met een ACS kan het CRP helpen om de kans in te schatten van een cardiale gebeurtenis in de toekomst. In één studie leek het CRP aanvankelijk gerelateerd aan de infarctgrootte en de mortaliteit bij patiënten die een primaire PCI ondergaan, doch na multivariabele analyse waren alleen troponine en Killip-klasse onafhankelijke voorspellers van mortaliteit. Stijging van het CRP na een electieve PCI lijkt echter ook een voorspellende waarde te hebben.

Het heart-type fatty acid binding protein (H-FABP) is een veelbelovende cardiale marker die snel uit de myocardcel vrijkomt bij myocardiale schade. Het lijkt qua kinetiek en uitstootprofiel op myoglobine, maar is cardiospecifieker. Recent is aangetoond dat H-FABP significant toegevoegde waarde heeft bij de

risicostratificatie van patiënten met een ACS, onafhankelijk van troponine, BNP en myoglobine. H-FABP is bruikbaar als marker van reperfusiesucces bij patiënten met een STEMI, zowel bij behandeling met trombolyse als bij behandeling met primaire PCI. Er zijn geen gegevens over de prognostische waarde van H-FABP na een electieve PCI. Mogelijk is het H-FABP bruikbaar bij patiënten waarbij een vroeg ontslag uit het ziekenhuis gepland is. Recent is echter aangetoond dat dit vroege ontslag ook reeds veilig kan op geleide van symptomen, angiografisch resultaat en het ECG, zonder cardiale markers als selectiecriterium. Toekomstige studies zullen de potentiële voordelen van het H-FABP moeten aantonen, maar het grootste voordeel is wellicht bij triage van patiënten met verdenking op een ACS.

# Curriculum Vitae

Marcus Bernardus Nienhuis werd op 23 juni 1974 geboren te Deventer. Hij groeide op in Raalte en behaalde daar het eindexamen VWO in 1992 aan het Florens Radewijns college. Na een jaar economie gestudeerd te hebben deed hij de opleiding geneeskunde aan de Rijksuniversiteit Groningen, welke hij eind 1999 afrondde. Van 2000 tot begin 2001 werkte hij als arts-assistent op de afdeling cardiologie in het Martini ziekenhuis te Groningen. In het jaar 2001 ging hij werken als arts-assistent cardiologie in de Isala klinieken te Zwolle. Daar begon hij in 2002 met de opleiding tot cardioloog, welke hij eind juni 2008 zal afronden. Naast de opleiding heeft hij zich in Zwolle ook bezig gehouden met onderzoek op het gebied van cardiale markers rondom een dotterbehandeling, wat geleid heeft tot dit proefschrift. Hij is in 2006 getrouwd met Anna Tomàs Farré.

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Dr. H. Suryapranata is een meester in het organiseren en opzetten van onderzoek en zelfs een geheel nieuw ziekenhuis, blijkens het succes in Jakarta. Dank voor de kritische noten bij de eerste versies van onze artikelen.
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